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(71) BAYER AKTIENGESELLSCHAFT,
D 61369, LEVERKUSEN, XX (DE).

(72)

WICK, MARESA (DE).
HAGEN, GUSTAV (DE).
ZUBOV, DMITRY (DE).

(74)

FETHERSTONHAUGH & CO.

- (54) SEQUENCES D'ADN REGULATRICES DU GENE DE LA SOUS-UNITE TELOMERASE CATALYTIQUE HUMAINE ET LEUR UTILISATION A DES FINS DIAGNOSTIQUES ET THERAPEUTIQUES
(54) REGULATORY DNA SEQUENCES OF THE HUMAN CATALYTIC TELOMERASE SUB-UNIT GENE, DIAGNOSTIC AND THERAPEUTIC USE THEREOF

(57)

The present invention relates to regulatory DNA sequences containing promoter sequences, in addition to intervening sequences, for the human catalytic telomerase sub-unit gene. The invention also relates to the use of said DNA sequences for pharmaceutical, diagnostic and therapeutic purposes, especially in the treatment of cancer and ageing.



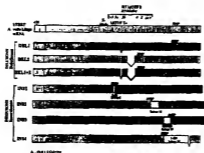
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(54) Title: REGULATORY DNA SEQUENCES OF THE HUMAN CATALYTIC TELOMERASE SUB-UNIT GENE, DIAGNOSTIC AND THERAPEUTIC USE THEREOF

(54) Bezeichnung: REGULATORISCHE DNA-SEQUENZEN DES GENS DER HUMANEN KATALYTISCHEN TELOMERASE-UNTEREINHEIT UND DEREN DIAGNOSTISCHE UND THERAPEUTISCHE VERWENDUNG



(57) Abstract

The present invention relates to regulatory DNA sequences containing promoter sequences, in addition to intervening sequences, for the human catalytic telomerase sub-unit gene. The invention also relates to the use of said DNA sequences for pharmaceutical, diagnostic and therapeutic purposes, especially in the treatment of cancer and ageing.

Le A 32 805-Foreign Countries/ Sto/Kr/Ke/NTRegulatory DNA sequences of the gene for the human catalytic telomerase subunit, and their diagnostic and therapeutic useStructure and function of the chromosome ends

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The genetic material of eukaryotic cells is distributed on linear chromosomes. The ends of hereditary units are termed telomeres, derived from the Greek words *telos* (end) and *meros* (part, segment). Most telomeres consist of repeats of short sequences which are mainly composed of thymine and guanine (Zakian, 1995). In all the vertebrates which have so far been investigated, the telomeres consist of the sequence TTAGGG (Meyne *et al.*, 1989).

10

The telomeres have a variety of important functions. They prevent the fusion of chromosomes (McClintock, 1941) and thus the formation of dicentric hereditary units. Such chromosomes having two centromeres can lead to the development of cancer due to loss of heterozygosis or duplication, or loss of genes.

15

In addition, telomeres serve the purpose of distinguishing intact hereditary units from damaged hereditary units. Thus, yeast cells ceased their cell division when they contained a chromosome without a telomere (Sandell and Zakian, 1993).

20

Telomeres fulfil another important task in association with the replication of eukaryotic cell DNA. In contrast to the circular genomes of prokaryotes, the linear chromosomes of eukaryotes cannot be completely replicated by the DNA polymerase complex. RNA primers are required to initiate DNA replication. After elimination of the RNA primers, extension of the Okazaki fragments and subsequent ligation, the newly synthesized DNA strand lacks the 5' end since the RNA primer cannot be replaced by DNA at that point. Without special protective mechanisms, the chromosomes would therefore shrink with each cell division ("end-replication problem"; Harley *et al.*, 1990). The non-coding telomere sequences presumably constitute a buffer zone for preventing the loss of genes (Sandell and Zakian, 1993).

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In addition to this, telomeres also play an import role in regulating cell ageing (Olovnikov, 1973). Human somatic cells exhibit a limited capacity for replication in culture; after a certain period of time, they become senescent. In this state, the cells no longer divide even after having been stimulated with growth factors; however, they do not die and remain metabolically active (Goldstein, 1990). Various observations support the hypothesis that a cell determines how many more times it can divide on the basis of the length of its telomeres (Allsopp *et al.*, 1992).

In summary, the telomeres consequently possess key functions in the ageing of cells, and in stabilizing the genetic material and preventing cancer.

The enzyme telomerase synthesizes the telomeres

As described above, organisms which possess linear chromosomes can only replicate their genome incompletely in the absence of a special protective mechanism. Most eukaryotes use a special enzyme, i.e. telomerase, for regenerating the telomere sequences. Telomerase is expressed constitutively in the single-cell organisms which have so far been investigated. On the other hand, telomerase activity has only been measured in humans in germ cells and tumour cells, whereas neighbouring somatic tissue did not contain any telomerase (Kim *et al.*, 1994).

Telomerase can also be designated functionally as terminal telomere transferase, which is located in the cell nucleus as a multiprotein complex. While the RNA moiety of human telomerase has been known for a relatively long period of time (Feng *et al.*, 1995), the catalytic subunit of this enzyme group was recently identified in a variety of organisms (Lingner *et al.*, 1997; cf. our application PCT EP/98/03468 which is likewise pending). These catalytic subunits of telomerase are strikingly homologous both among themselves and in relation to all previously known reverse transcriptases.

WO 98/14592 also describes nucleic acid and amino acid sequences of the catalytic telomerase subunit

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Activation of telomerase in human tumours

It was originally only possible to demonstrate telomerase activity in humans in germ line cells and not in normal somatic cells (Hastie *et al.*, 1990; Kim *et al.*, 1994). Following the development of a more sensitive detection method (Kim *et al.*, 1994), a low telomerase activity was also detected in hematopoietic cells (Broccoli *et al.*, 1995; Counter *et al.*, 1995; Hiyama *et al.*, 1995). It is true, however, that these cells nevertheless exhibited a reduction in the telomeres (Vaziri *et al.*, 1994; Counter *et al.*, 1995). It has still not been resolved whether the quantity of enzyme in these cells is not sufficient for compensating the telomere loss or whether the telomerase activity which is measured stems from a subpopulation, e.g. incompletely differentiated CD34⁺38⁺ precursor cells (Hiyama *et al.*, 1995). In order to resolve this, it would be necessary to detect telomerase activity in a single cell.

Interestingly, however, significant telomerase activity was detected in a large number of the tumour tissues which had thus far been tested (1734/2031, 85%; Shay, 1997), whereas no activity was found in normal somatic tissue (1/196, <1%, Shay, 1997). In addition various investigations have shown that the telomeres still shrank in senescent cells which were transformed with viral oncoproteins and it was only possible to detect telomerase in the subpopulation which survived the growth crisis (Counter *et al.*, 1992). The telomeres were also stable in these immortalized cells. (Counter *et al.*, 1992). Similar findings from investigations in mice (Blasco *et al.*, 1996) support the assumption that reactivation of the telomerase is a late event in tumorigenesis.

Based on these results, a "telomerase hypothesis" was developed which links the loss of telomere sequences and cell ageing with telomerase activity and the development of cancer. In long-lived species such as humans, the shrinking of the telomeres can be regarded as being a mechanism for suppressing tumours. Differentiated cells which do not contain any telomerase cease their cell division at a particular telomere length. If such a cell mutates, it can only form a tumour if the cell can extend its telomeres.

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Otherwise, the cell would continue to lose telomere sequences until its chromosomes became unstable and it was finally destroyed. Telomerase reactivation is presumably the main mechanism used by tumour cells to stabilize their telomeres.

5 It follows from these observations and considerations that it should be possible to treat tumours by inhibiting the telomerase. Conventional cancer therapies using cytostatic agents or short-wave radiation damage all the dividing cells in the body in addition to the tumour cells. However, since only germ line cells, apart from tumour cells, contain significant telomerase activity, telomerase inhibitors would attack the
10 tumour cells more specifically and consequently elicit fewer undesirable side effects. Telomerase activity has been detected in all the tumour tissues which have so far been tested, which means that these therapeutic agents could be employed against all types of cancer. The effect of telomerase inhibitors would then set in when the telomeres of the cells had shortened to such an extent that the genome became
15 unstable. Since tumour cells usually possess telomeres which are shorter than those of normal somatic cells, cancer cells would be the first to be eliminated by the telomerase inhibitors. By contrast, cells possessing long telomeres, such as the germ cells, would only be damaged at a much later date. Telomerase inhibitors consequently represent a potential way forward in the treatment of cancer.

20 It becomes possible to obtain unambiguous answers to the question of the nature and points of attack of physiological telomerase inhibitors once the manner in which expression of the telomerase gene is regulated has also been identified.

25 Regulation of gene expression in eukaryotes

There are a large number of points in eukaryotic gene expression, i.e. the cellular flow of information from the DNA to the protein by way of the RNA, at which regulatory mechanisms can exert an effect. Examples of individual control steps are
30 gene amplification, the recombination of gene loci, chromatin structure, DNA methylation, transcription, post-transcriptional modifications of mRNA, mRNA transport, translation and post-translational modifications of proteins. Studies which

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have been carried out to date indicate that control at the level of transcription initiation is of the greatest importance (Latchman, 1991).

- 5 A region which is responsible for regulating transcription, and which is designated the promoter region, is located directly upstream of the transcription start of a gene which is transcribed by RNA polymerase II. Comparison of the nucleotide sequences of promoter regions from a large number of known genes shows that particular sequence motifs occur regularly in this region. These elements include, inter alia, the TATA box, the CCAAT box and the GC box, which elements are recognized by
- 10 specific proteins. The TATA box, which is located about 30 nucleotides upstream of the transcription start, is, for example, recognized by the TFIID subunit TBP ("TATA box-binding protein"), whereas particular GC-rich sequence segments are specifically bound by the transcription factor Sp1 ("specificity protein1").
- 15 The promoter can be functionally subdivided into a regulatory segment and a constitutive segment (Latchman, 1991). The constitutive control region comprises the so-called core promoter which enables transcription to be initiated correctly. This promoter contains the sequence elements which are described as UPE's (upstream promoter elements) which are necessary for efficient transcription. The regulatory
- 20 control segments, which can be interlaced with the UPE's, possess sequence elements which can be involved in the signal-dependent regulation of transcription by hormones, growth factors, etc. They impart tissue-specific or cell-specific promoter properties.
- 25 DNA segments which are able to exert an influence on gene expression over relatively large distances are a characteristic feature of eukaryotic genes. These elements can be located upstream or downstream of a transcription unit, or within the unit, and can perform their function independently of their orientation. These sequence segments may reinforce (enhancers) or attenuate (silencers) promoter
- 30 activity. In a similar way to the promoter regions, enhancers and silencers also accommodate several binding sites for transcription factors.

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The invention relates to the DNA sequences from the 5'-flanking region of the gene for the catalytically active human telomerase subunit and intron sequences for this gene.

- 5 The invention particularly relates to the 5'-flanking regulatory DNA sequence which contains the promoter DNA sequence for the gene for the human catalytic telomerase subunit, as depicted in Fig. 10 (SEQ ID NO 3).

10 The invention furthermore relates to part regions of the 5'-flanking regulatory DNA sequence, as depicted in Fig. 4 (SEQ ID NO 1), which has a regulatory effect.

Intron sequences for the gene for the human catalytic telomerase subunit, in particular those sequences which have a regulatory effect, are also part of the subject-matter of the present invention. The intron sequences according to the invention are described in detail in the context of Example 5 (cf. SEQ ID NO 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20).

20 The invention furthermore relates to a recombinant construct which comprises the DNA sequences according to the invention, in particular the 5'-flanking DNA sequence of the gene for the human catalytic telomerase subunit, or part regions thereof.

25 Preference is given to recombinant constructs which, in addition to the DNA sequences according to the invention, in particular the 5'-flanking DNA sequence of the gene for the human catalytic telomerase subunit, or part regions thereof, also contain one or more additional DNA sequences which encode polypeptides or proteins.

30 According to a particularly preferred embodiment, these additional DNA sequences encode antineoplastic proteins.

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Particular preference is given to those antineoplastic proteins which inhibit angiogenesis directly or indirectly. Examples of these proteins are:

- 5 Plasminogen activator inhibitor (PAI-1), PAI-2, PAI-3, angiostatin, endostatin, platelet factor 4, TIMP-1, TIMP-2, TIMP-3 and leukaemia inhibitory factor (LIF).

Antineoplastic proteins which have a direct or indirect cytostatic effect on tumours are likewise particularly preferred. These proteins include, in particular:

- 10 perforin, granzyme, IL-2, IL-4, IL-12, interferons, such as IFN- α , IFN- β and IFN- γ , TNF, TNF- α , TNF- β , oncostatin M; tumour suppressor genes, such as p53, retinoblastoma.

- 15 Particular preference is furthermore given to antineoplastic proteins which, where appropriate in addition to their antineoplastic effect, stimulate inflammations and thereby contribute to the elimination of tumour cells. Examples of these proteins are:

- 20 RANTES, monocyte chemoattractant and activating factor (MCAF), IL-8, macrophage inflammatory protein (MIP-1 α , - β), neutrophil activating protein-2 (NAP-2), IL-3, IL-5, human leukaemia inhibitory factor (LIF), IL-7, IL-11, IL-13, GM-CSF, G-CSF and M-CSF.

- 25 Particular preference is furthermore given to antineoplastic proteins which, due to their action as enzymes, are able to convert precursors of an antineoplastic active compound into an antineoplastic active compound. Examples of these enzymes are:

- herpes simplex virus thymidine kinase, varicella zoster virus thymidine kinase, bacterial nitroreductase, bacterial β -glucuronidase, plant β -glucuronidase from *Secale cereale*, human glucuronidase, human carboxypeptidase, bacterial carboxypeptidase, 30 bacterial β -lactamase, bacterial cytosine deaminase, human catalase and/or phosphatase, human alkaline phosphatase, type 5 acid phosphatase, human

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lysooxidase, human acid D-aminooxidase, human glutathione peroxidase, human eosinophil peroxidase and human thyroid peroxidase.

5 The abovementioned recombinant constructs can also contain DNA sequences which encode factor VIII or factor IX, or part fragments thereof. These DNA sequences also include other blood clotting factors.

The abovementioned recombinant constructs can also contain DNA sequences which encode a reporter protein. Examples of these reporter proteins are:

10 Chloramphenicol acetyl transferase (CAT), glow-worm luciferase (LUC), β -galactosidase (β -Gal), secreted alkaline phosphatase (SEAP), human growth hormone (hGH), β -glucuronidase (GUS), green-fluorescing protein (GFP), and all the variants derived therefrom, aquarin and obelin.

15 Recombinant constructs according to the invention can also contain DNA which encodes the human catalytic telomerase subunit and its variants and fragments in the antisense orientation. Where appropriate, these constructs can also contain other protein subunits of the human telomerase and the telomerase RNA component in the antisense orientation.

20 The recombinant constructs can, in addition to the DNA which encodes the human catalytic telomerase subunit, and its variants and fragments, also contain other protein subunits of the human telomerase and the telomerase RNA component.

25 The invention furthermore relates to a vector which contains the abovementioned DNA sequences according to the invention, in particular the 5'-flanking DNA sequences and also one or more of the other DNA sequences mentioned above.

30 The preferred vector for these constructs is a virus, for example a retrovirus, an adenovirus, an adeno-associated virus, a herpes simplex virus, a vaccinia virus, a lentiviral virus, a Sindbis virus and a Semliki forest virus.

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Preference is also given to using plasmids as vectors.

5 The invention furthermore relates to pharmaceutical preparations which comprise recombinant constructs or vectors according to the invention; for example a preparation in a colloidal dispersion system.

10 Examples of suitable colloidal dispersion systems are liposomes or polylysine ligands.

The preparations of the constructs or vectors according to the invention in colloidal dispersion systems can be supplemented with a ligand which binds to the membrane structures of tumour cells. Such a ligand can, for example, be attached to the construct or the vector or else be a component of the liposome structure.

15 Suitable ligands are, in particular, polyclonal or monoclonal antibodies, or antibody fragments thereof, which bind, by their variable domains, to the membrane structures of tumour cells, or substances carrying mannose terminally, cytokines or growth factors, or fragments or part sequences thereof, which bind to receptors on tumour cells.

20 Examples of corresponding membrane structures are receptors for a cytokine or a growth factor, such as IL-1, EGF, PDGF, VEGF, TGF β , insulin or insulin-like growth factor (IGF), or adhesion molecules, such as SLeX, LFA-1, MAC-1, LECAM-1 or VLA-4, or the mannose-6-phosphate receptor.

25 The present invention includes pharmaceutical preparations which, in addition to the vector constructs according to the invention, can also comprise non-toxic, inert, pharmaceutically suitable excipients. It is possible to conceive of administering (e.g. 30 intravenously, intraarterially, intramuscularly, subcutaneously, intradermally, anally, vaginally, nasally, transdermally, intraperitoneally, as an aerosol or orally) these preparations at the site of a tumour or administering them systemically.

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The vector constructs according to the invention can be employed in gene therapy.

5 The invention furthermore relates to a recombinant host cell, in particular a recombinant eukaryotic host cell, which harbours the above-described constructs or vectors.

10 The invention furthermore relates to a process for identifying substances which affect the promoter activity, silencer activity or enhancer activity of the catalytic telomerase subunit, with this process comprising the following steps:

15 A. adding a candidate substance to a host cell which harbours the regulatory DNA sequence according to the invention, in particular the 5'-flanking regulatory DNA sequence for the gene for the human catalytic telomerase subunit, or a part region thereof which has a regulatory effect, which sequence or part region is functionally linked to a reporter gene, and

B. measuring the effect of the substance on expression of the reporter gene.

20 The process can be employed for identifying substances which increase the promoter activity, silencer activity or enhancer activity of the catalytic telomerase subunit.

25 The process can furthermore be employed for identifying substances which inhibit the promoter activity, silencer activity or enhancer activator of the catalytic telomerase subunit.

30 The invention furthermore relates to a process for identifying factors which bind specifically to fragments of the DNA fragments according to the invention, in particular the 5'-flanking regulatory DNA sequence of the catalytic telomerase subunit. This method comprises screening an expression cDNA library using the above-described DNA sequence, or subfragments of widely differing length, as the probe.

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The above-described constructs or vectors can also be used for preparing transgenic animals.

5 The invention furthermore relates to a process for detecting telomerase-associated conditions in a patient, which process comprises the following steps:

A. incubating a construct or vector, which contains the DNA sequence according to the invention, in particular the 5'-flanking regulatory DNA sequence for the
10 gene for the human catalytic telomerase subunit, or a part region thereof having a regulatory effect, and a reporter gene, with body fluids or cell samples,

B. detecting the activity of the reporter gene in order to obtain a diagnostic value;
15 and

C. comparing the diagnostic value with standard values for the reporter gene construct in standardized normal cells or body fluids of the same type as the
20 test sample;

The detection of diagnostic values which are higher or lower than the standard comparative values indicates a telomerase-associated condition, which in turn indicates a pathogenic condition.

25 Explanation of the figures:

Fig. 1: Southern blot analysis using genomic DNA from various species

30 A: Photograph of an ethidium bromide-stained 0.7% agarose gel containing approximately 4 µg of Eco RI-cut genomic DNA. Track 1 contains Hind III-cut λ DNA as size markers (23.5, 9.4, 6.7, 4.4, 2.3, 2.0 and 0.6 kb). Tracks 2 to 10 contain human, rhesus monkey, Sprague

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Dawley rat, BALB/c mouse, dog, bovine, rabbit, chicken and yeast (*Saccharomyces cerevisiae*) genomic DNA.

B: Autoradiogram, corresponding to Fig. 1 A, of a Southern blot analysis in which radioactively labelled hTC-cDNA probe of about 720 bp in length is used for the hybridization.

Fig. 2: Restriction analysis of the recombinant λ DNA of the phage clone P12, which hybridizes with a probe from the 5' region of the hTC cDNA.

The figure shows a photograph of an ethidium bromide-stained 0.4% agarose gel. Tracks 1 and 2 contain Eco RI/Hind III-cut λ DNA and a 1 kb ladder from Gibco as size markers. Tracks 3 - 7 each contain 250 ng of the DNA from the recombinant phage which has been cut with Bam HI (track 3), Eco RI (track 4), Sal I (track 5), Xho I (track 6) and Sac I (track 7). The arrows mark the two λ arms of the vector EMBL3 Sp6/T7.

Fig. 3: Restriction analysis and Southern blot analysis of the recombinant λ DNA of the phage clone which hybridizes with a probe from the 5' region of the hTC cDNA.

A: The figure shows a photograph of an ethidium bromide-stained 0.8% agarose gel. Tracks 1 and 15 contain a 1 kb ladder from Gibco as size markers. Tracks 2 to 14 each contain 250 ng of cut λ DNA from the recombinant phage clone. The following enzymes were employed: track 2: Sac I, track 3: Xho I, track 4: Xho I, Xba I, track 5: Sac I, Xho I, track 6: Sal I, Xho I, Xba I, track 7: Sac I, Xho I, Xba I, track 8: Sac I, Sal I, Xba I, track 9: Sac I, Sal I, BamH I, track 10: Sac I, Sal I, Xho I, track 11: Not I, track 12: Sma I, track 13: empty, track 14: not digested.

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B: Autoradiogram, corresponding to Fig. 3 A, of a Southern blot analysis. A 5'-hTC cDNA fragment of about 420 bp in length was used as the probe for the hybridization.

5 Fig. 4: Partial DNA sequence of the 5'-flanking region and of the promoter of the gene for the human catalytic telomerase subunit. The ATG start codon in the sequence is printed in bold. The depicted sequence corresponds to SEQ ID NO 1.

10 Fig. 5: Use of primer extension analysis to identify the transcription start.

The figure shows an autoradiogram of a denaturing polyacrylamide gel which was selected for depicting a primer extension analysis. An oligonucleotide having the sequence
 15 5' GTTAAGTTGTAGCTTACACTGGTTCTC 3' was used as the primer. The primer extension reaction was loaded in track 1. Tracks G, A, T and C constitute the sequence reactions using the same primer and the corresponding dideoxynucleotides. The thick arrow marks the main transcription start while the thin arrows point to three subsidiary transcription start points.
 20

Fig. 6: cDNA sequence of the human catalytic telomerase subunit (hTC; cf. our pending application PCT/EP/98/03468). The depicted sequence corresponds to SEQ ID NO 2.
 25

Fig. 7: Structural organization and restriction map of the human hTC gene and its 5'-flanking and 3'-flanking regions.

Exons are shown as consecutively numbered rectangles which are filled-in in black, and introns are shown as regions which are not filled in. Untranslated sequence segments in the exons are hatched. Translation starts in exon 1 and ends in exon 16. Restriction enzyme cleavage sites
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are marked as follows: S, SacI; X, XhoI. The relative arrangement of the five phage clones (P2, P3, P5, P12, P17), and of the product from the genome walking, are shown by thin lines. As the dots indicate, the sequence of intron 16 has only been partly deciphered.

Fig. 8: HTL splice variants.

A: Diagrammatic structure of the hTC mRNA splice variants. The complete hTC mRNA is depicted as a rectangle with a grey background in the upper region of the figure. The 16 exons are depicted in accordance with their size. The translation start (ATG) and the stop codon, and also the telomerase-specific T motif, and the seven RT motifs, are all shown. The hTC variants are subdivided into deletion and insertion variants. The missing exon sequences are marked in the deletions. The insertions are shown by additional white rectangles. The sizes and origins of the inserted sequences are given. Newly formed stop codons are marked. The size of the insertion in variant INS2 is unknown.

B: Exon-intron transitions in the hTC splice variants. Unspliced 5'-flanking and 3'-flanking sequences are shown as white rectangles. The origins of the exon and intron sequences are given. Intron and exon sequences are shown in small letters and large letters, respectively. The donor and acceptor sequences in the splice sites are underlaid as grey rectangles, and their exon and intron origins are also given.

Fig. 9 Identification of the transcription start by means of RT-PCR analysis.

The RT-PCR was carried out using a cDNA library prepared from HL 60 cells and genomic DNA as the positive control. A common 3' primer hybridizes to a region of the exon 1 sequence. The positions of the different 5' primers in the coding region or the 5'-flanking region are given. In the negative control, no template DNA was added to the PCR reaction. M: DNA size marker.

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Fig. 10: Nucleotide sequence and structural features of the hTC promoter.

The figure depicts 11273 bp of the 5'-flanking hTC gene sequence, beginning with the translation start codon ATG (+1). The putative region of the translation start is underlined. Possible regulatory sequence segments within the 4000 bp upstream of the translation start are ringed. The depicted sequence corresponds to SEQ ID NO 3.

Fig. 11: Activity of the hTC promoter in HEK-293 cells.

The first 5000 bp of the 5'-flanking hTC gene region are shown diagrammatically in the upper part of the figure. The ATG start codon is picked out. CpG-rich islands are marked by grey rectangles. The sizes of the hTC promoter-luciferase construct are shown on the left-hand side of the figure. The promoterless pGL2 basic construct and the SV40 promoter construct pGL2-Pro were used as controls in each transfection. The relative luciferase activities of the different promoter constructs in HEK cells are shown as continuous bars on the right-hand side of the figure. The standard deviation is indicated. The numerical values represent the average of two independent experiments which were carried out in duplicate.

Tab. 1: Exon-intron transitions in the hTC gene

The table lists the nucleotide sequences at the 3' and 5' splice transitions of the hTC gene. The consensus sequences for donor and acceptor sequences (AG and GT) are underlined with grey rectangles. The table shows the intron sequences (small letters) and exon sequences (large letters) which flank the splice acceptor and donor sites. The sizes of the exons and introns are given in bp.

Tab. 2: Potential binding sites for DNA-binding factors in the nucleotide sequence of intron 2

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The search for possible DNA-binding factors (e.g. transcription factors) was carried out using the "find pattern" algorithm from the Genetics Computer Group (Madison, USA) GCG sequence analysis program package. The table lists the abbreviations of the DNA-binding factors which were identified and their location in intron 2.

Tab. 1

3' Acceptor Sequence

5' Donor Sequence

Intron	Exon	Exon No.	bp	Exon	Intron	Intron No.	bp
5' flanking region	GTTCACGACGACGCTGCTG	1	281	CGCCCTCTCTCTCCGACG	gtaggctcccgaggtg	1	104
cgagggagctcccgag	GTGTCTTGGCTGAGGAC	2	1354	TGCTCTGCGAGGACGACG	gtagggaggtgtagcgt	2	8616
catgactctctctttag	GGCTTGGCTGCTGCTGCGG	3	196	TGCAGAGCATTCGAGACG	gtagctgatacccgagca	3	2089
gagggagctctctctttag	ACAGCATTCGAGAGGCTG	4	181	GTTCGCGAGGAGAGAGG	gtagcgtgcttctgttta	4	687
cccatgctgctcccgctag	GCAGAGCTCTCACCTCGA	5	180	TGAGCTGTACTTCTCGAG	gtagggtagcgggagccccc	5	494
ctcgcctccactccacag	GTGCTAGTTCAGGCGGCTG	6	156	CAGGCTTTCAGAGCGGAC	gtagggttcaagctgtagta	6	>4660
ccctctctctctcgagag	GTCTTACCTTGACAGACC	7	96	TCCCTCTGCTATCGAGCG	gtagtggcaactgacgtaca	7	980
ctccgctctgcttttag	AGCTCTCTCTGAGATGAG	8	86	CGCTGCGCATTCAGGAGGCA	gtagtgcaggtgagcaggt	8	2485
ctgtgtctctcccgccag	GTCTTACCTTCAGGTGCCAG	9	114	CGGAGATTTCGCGGACGG	gtaggagctctctctccgc	9	1984
gatttctctctcttttag	GTCTCTCTCTCTGCTTGGTG	10	72	ACCGAGAGAGCTTCTCTGAG	gtagggagctctctctctccgc	10	1871
ctctccctctctctcttag	GACTCTCTCTCTGAGAGGCTC	11	189	TGCGAGGAGGCTTCTCTGAG	gtagggagctctctctctccgc	11	3801
ctctccctctctctcttag	CTATGCGCGGAGCTCTGATC	12	127	CGCTTCTCTGAGATTCTGAG	gtagggagctctctctctccgc	12	880
ctctctctctctctcttag	GTTCAGGAGCTCTGAGGCTC	13	62	TCTCTCTCTGAGGCTCTGAG	gtagggagctctctctctccgc	13	3187
ctctctctctctctcttag	GTTCAGGAGCTCTGAGGCTC	14	125	CTGAGGAGCTCTGAGGCTC	gtagggagctctctctctccgc	14	781
ctctctctctctctcttag	GTTCAGGAGCTCTGAGGCTC	15	138	CTGAGGAGCTCTGAGGCTC	gtagggagctctctctctccgc	15	536
ctctctctctctctcttag	GTTCAGGAGCTCTGAGGCTC	16	664	TTCCTCTCTCTGAGGCTC	gtagggagctctctctctccgc	16	536
ctctctctctctctcttag	GTTCAGGAGCTCTGAGGCTC	17	664	TTCCTCTCTCTGAGGCTC	gtagggagctctctctctccgc	17	536

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Tab. 2

Factors	Location in Intron 2
C/EBP	2925
CRE.2	2749
Sp1	2378, 4094, 4526, 4787, 4835, 4995
AP-2 CS3	5099
AP-2 CS4	2213, 3699, 4667, 5878, 5938, 6059, 6180, 6496
AP-2 CS5	5350, 5798, 5880, 5940, 6061, 6182, 6375, 6498
PEA3	934, 2505
P53	2125
GR uteroglobin	848, 1487, 2956
PR uteroglobin	3331
Zeste-white	1577, 1619, 1703, 1745, 1787, 1829, 1871, 1913, 1955, 1997, 2039, 2081, 3518, 3709, 4765, 5014, 5055
GRE	846
MyoD-MCK right site/rev	447, 509, 558, 1370, 1595, 1900, 2028, 2099, 4557
MyoD-MCK left site	108, 118, 453, 1566, 1608, 1692, 1734, 1818, 1902, 1986, 2372, 2460, 2720, 3491, 5030
Ets-1 CS	6408
AP1	3784, 4406
CREB	2801
GATA-1	839, 1390, 3154
c-Myc	108, 118, 453, 1566, 1608, 1692, 1734, 1818, 1902, 1986, 2372, 2460, 2720, 3491, 5030
CACCC site	991
CCAAT site	1224
CCAC box	992
CAAT site	463, 2395
Rb site	992, 4663
TATA	3650
CDEI	106, 1564, 1606, 1690, 1732, 1816, 1900, 1984

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Examples

The human gene for the catalytic telomerase subunit (ghTC), and the regions of this gene located 5' and 3', were cloned, while the start point for transcription was determined, potential binding sites for DNA-binding proteins were identified and active promoter fragments were highlighted. The sequence of the hTC cDNA (Fig. 6) has already been reported in our application PCT/EP/98/03468, which is also pending. Unless otherwise mentioned, all the data refer to the position of the cDNA in this sequence.

Example 1

A genomic Southern blot analysis was used to determine whether ghTC constitutes a single gene in the human genome or whether there exist several loci for the hTC gene and possibly also ghTC pseudogenes.

In order to do this, a commercially available zoo blot from Clontech was subjected to Southern blot analysis. This blot contains 4 µg of Eco RI-cut genomic DNA from nine different species (human, monkey, rat, mouse, dog, bovine, rabbit, chicken and yeast). With the exception of yeast, chicken and human, the DNA was isolated from kidney tissue. The human genomic DNA was isolated from placenta and the chicken genomic DNA was purified from liver tissue. An hTC cDNA fragment of about 720 bp in length, which was isolated from hTC cDNA, variant Del2 (position 1685 to 2349 plus 2531 to 2590 in Fig. 6 [deletion 2; cf. Example 5 in Fig. 8]), was used as the radioactively labelled probe in the autoradiogram in Fig. 1. The experimental conditions for the blot hybridization and washing steps were taken from Ausubel *et al.* (1987).

In the case of the human DNA, the probe recognizes two specific DNA fragments. The smaller Eco RI fragment, of from about 1.5 to 1.8 kb in length, probably originates from two Eco RI cleavage sites in an intron in the ghTC DNA. On the

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basis of this result, it is to be assumed that only one single ghTC gene is present in the human genome.

Example 2

5

In order to isolate the 5' flanking hTC gene sequence, approx. 1.5×10^6 phages from a human genomic placenta gene library (EMBL 3 SP6/T7 from Clontech, order number HL1067j) were hybridized on nitrocellulose filters (0.45 μm ; from Schleicher and Schuell), in accordance with the manufacturer's instructions, with a radioactively labelled 5'-hTC cDNA fragment of about 500 bp in length (position 839 to 1345 in Fig. 6). The nitrocellulose filters were firstly incubated, at 42°C for two hours, in 2 x SSC (0.3 M NaCl; 0.5 M Tris-HCl, pH 8.0) and then in a prehybridization solution (50% formamide; 5 x SSPE, pH 7.4; 5 x Denhard's solution; 0.25% SDS; 100 μg of herring sperm DNA/ml). For the overnight hybridization, the prehybridization solution was supplemented with 1.5×10^6 cpm of denatured, radioactively labelled probe/ml of solution. Nonspecifically bound radioactive DNA was removed under stringent conditions, i.e. by means of three five-minute steps of washing with 2 x SSC; 0.1% SDS at from 55 to 65°C. The filters were evaluated by autoradiography.

20

The phage clones which were identified in this primary investigation were purified (Ausubel *et al.* (1987)). In subsequent analyses, one phage clone, i.e. P12 turned out to be potentially positive. A λ DNA preparation carried out on this phage (Ausubel *et al.* (1987)), and the subsequent restriction digestion with enzymes which release the genomic insert in fragments, showed that this phage clone contains an insert of approx. 15 kb in the vector (Fig. 2).

25

In order to isolate the complete hTC gene sequence, in each case from 1 to 1.5×10^6 phages were screened, in independent experiments, with in each case different radioactively labelled probes, as described above.

30

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The phage clones which were identified in these primary investigations, and which were positive for the corresponding probes, were purified. The phage clone P17 was found to contain an hTC cDNA fragment of about 250 bp in length (position 1787 to 2040 in Fig. 6). The phage clone P2 was identified as containing an hTC cDNA
5 fragment of about 740 bp in length (position 1685 to 2349 plus 2531 to 2607 in Fig. 6 [deletion 2; cf. Example 5]). The phage clones P3 and P5 were found to contain a 3' hTC cDNA fragment of 420 bp in length (position 3047 to 3470 in Fig. 6). After the λ DNA had been prepared from these phages, and subsequently subjected to restriction digestion with enzymes which release the genomic insert in fragments, the
10 inserts were subcloned into plasmids (Example 4).

Example 3

In order to investigate whether the 5' end of the hTC cDNA was also present in the
15 insert in the recombinant phage clone P12, the λ DNA from this clone was hybridized, in a Southern blot analysis, with a radiactively labelled hTC cDNA fragment of about 440 bp in length (position 1 to 440 in Fig. 6) from the extreme 5' region (Fig. 3).

20 Since the isolated λ DNA from the positive clone also hybridizes with the extreme 5' end of the hTC cDNA, this phage probably also contains the 5' sequence region flanking the ATG start codon.

Example 4

25 In order to subclone the entire 15 kb insert in the positive phage clone P12 in the form of subfragments, and subsequently to sequence these fragments, restriction endonucleases which, on the one hand, release the entire insert from EMBL3 Sp6/T7 (cf. Example 2) and, in addition, cut within the insert, were selected for digesting the
30 DNA

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- In all, two Xho I subfragments, of about 8.3 and about 6.5 kb in length, respectively, and three Sac I subfragments, of about 8.5, about 3.5 and about 3 kb in length, respectively, were subcloned into the pBluescript KS(+) vector (from Stratagene). The 5123 bp 5'-flanking nucleotide sequence of the ghTC gene region, starting from the ATG start codon, was determined by analysing the sequences of these fragments (Fig. 4; corresponding to SEQ ID NO 1). Fig. 4 depicts the first 5123 bp (starting from the ATG start codon). Fig. 10 depicts the entire cloned 5' sequence (corresponding to SEQ ID NO 3).
- 10 In order to subclone the entire insert, of approx. 14.6 kb in size, in phage clone P17 in the form of subfragments, restriction endonucleases which, on the one hand, release the entire insert from EMLB3 Sp6/T7 and, in addition, cut a few times within the insert, were selected for digesting the DNA. Three XhoI/BamHI fragments, of 7.1 kb, 4.2 kb and 1.5 kb in size, respectively, and one BamHI fragment, of 1.8 kb in size, were subcloned by means of using a combination digestion with the enzymes XhoI and BamHI. Combination restriction digestion with the enzymes XhoI and XbaI resulted in a XhoI/XbaI fragment of 6.5 kb in size, and two XhoI fragments, of 6.5 kb and 1.5 kb in size, respectively, being cloned.
- 15 20 Digestion with the restriction enzyme XhoI was used to subclone the insert, of approx. 17.9 kb in size, in phage clone P2 in the form of subfragments. In all, three XhoI subfragments, of 7.5 kb, 6.4 kb and 1.6 kb in length, respectively, were cloned. Four SacI fragments, of 4.8 kb, 3 kb, 2 kb and 1.8 kb in size, respectively, were additionally subcloned by digesting with the restriction enzyme SacI.
- 25 The insert, of approx. 13.5 kb in size, in phage clone P3 was subcloned by digesting with the restriction enzymes SacI and/or XhoI. Six SacI subfragments, of 3.2 kb, 2 kb, 0.9 kb, 0.8 kb, 0.65 kb and 0.5 kb in length, respectively, and two XhoI subfragments, of 6.5 kb and 4.3 kb in length, respectively, were obtained in this connection.
- 30

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The insert, of approx. 13.2 kb in size, in phage clone P5 was subcloned by digesting with the restriction enzymes *SacI* and/or *XhoI*. In all, *SacI* fragments of 6.5 kb, 3.3 kb, 3.2 kb, 0.8 kb and 0.3 kb in size, and *XhoI* fragments of 7 kb and 3.2 kb in size, were subcloned.

5

In order to clone the hTC genomic sequence region located 3' of phage clone P17 and 5' of phage clone P2, 3 genomic walkings were carried out using the Clontech GenomeWalker™ kits (catalogue number K1803-1) and various combinations of primers. In a final volume of 50 µl, 10 pmol of dNTP mix were added to 1 µl of human GenomeWalker Library HDL (from Clontech), and a PCR reaction was carried out in 1xKlen Taq PCR reaction buffer and 1xAdvantage Klen Taq polymerase mix (from Clontech). 10 pmol of an internal gene-specific primer, and 10 pmol of the adaptor primer AP1 (5'-GTAATACGACTCACTATAGGGC-3'; from Clontech) were added as primers. The PCR was carried out in 3 steps as a touchdown PCR. First of all, denaturation was carried out at 94°C for 20 sec, and the primers were then annealed, and the DNA chain extended, at 72°C for 4 min, over 7 cycles. There then followed 37 cycles in which the DNA was denaturated at 94°C for 20 sec but the subsequent primer extension took place at 67°C for 4 min. In conclusion, there followed a chain extension at 67°C for 4 min. After this first PCR, the PCR product was diluted 1:50. One µl of this dilution was used in a second nested PCR together with 10 pmol of dNTP mix in 1xKlen Taq PCR reaction buffer and 1xAdvantage Klen Taq polymerase mix and also 10 pmol of a nested gene-specific primer and 10 pmol of the nested Marathon Adaptor primers AP2 (5'-ACTATAGGGCACGCGTGGT-3'; from Clontech). The PCR conditions corresponded to the parameters which were selected in the first PCR. As the sole exception, only 5 cycles rather than 7 cycles were selected in the first PCR step and only 24 cycles, instead of 37 cycles, were run in the second PCR step. The products of this nested genomic walking PCR were cloned into the TA Cloning Vector pCRII from InVitrogen.

30

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In the first genomic walking, the gene-specific primer C3K2-GSP1 (5'-GACGTGGCTCTTGAAGGCCTTG-3') and the nested gene-specific primer C3K2-GSP2 (5'-GCCTTCTGACACCGCATACC-3') were used, together with the HDL library 4, and a PCR fragment of 1639 bp in length was obtained. In the second genomic walking, a PCR fragment of 685 bp in length was amplified from the HDL library 4 using the gene-specific primer C3F2 (5'-CGTAGTTGAGCACGCTGAACAGTG-3') and the nested gene-specific primer C3F (5'-CCTTCACCCTCGAGGTGAGACGCT-3). The third genomic walking mixture, using the gene-specific primer DEL5-GSP1 (5'-GGTGGATGTGACGGGCGCGTACG-3') and the nested gene-specific primer C5K-GSP1 (5'-GGTATGCCGTGGTCCAGAAGGC-3'), led to a 924 bp PCR fragments being cloned from the HDL library 1. In all, 2100 bp of the genomic hTC region located 3' of phage clone P17 were identified using this genomic walking method (see Fig. 7).

The subcloned fragments, and the genomic walking products, were sequenced in single-stranded form. The Lasergene Biocomputing Software (DNASTAR Inc. Madison, Wisconsin, USA) was used to identify overlapping regions and form contigs. In all, 2 large contigs were assembled from the sequences collected from phage clones P12, P17, P2, P3 and P5, and also the sequence data from the genomic walking. Contig 1 consists of sequence data from phage clones P12 and P17 and the sequence data from the genomic walking. Contig 2 was put together from the sequences from phage clones P2, P3 and P5. Overlapping phage clone regions are shown diagrammatically in Fig. 7. The sequence data from the 2 contigs are shown below. The ATG start codon in contig 1 is underlined. The TGA stop codon is underlined in contig 2.

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Contig1:

	ACTTGAGGCC	AGAGATTCAA	GGCTAGGGTG	AGCCATGATT	GCACACACAC	AGCGCCAGCT	TGGTCACAGA	76
	ATGACACCTT	GTCTCAAAA	CAAGGAAA	ANTTGAATA	ATTTAAAGCA	TCCTCTCTGG	CCAGCAGT	140
5	TTAAATCAGT	AAATCAGAA	CAGAGGAT	TTTGAACAT	ATACACACAC	ATGAAATATC	AACTATATAC	210
	TCTTGATGA	CGAGTGAATC	AATGAGAA	TTAAAGAGGA	AATTGAUAAA	ATTATTATAC	CAAAATATAC	280
	CCGAAACATA	ACCTCTCAAA	ACCCAGGGA	TACACGAAA	GCAGTGTCTA	GRAGGAGATT	TATAGCTATA	350
	AGACGATCTA	TCAAAAAGAT	AGAAAGGCGA	GGCGAGTGG	CTCATGCTTC	TAATGCCAGC	ACTTTGGGAC	420
	GCACAGGCGG	CGAGATGCC	TGAGGTGAGC	AGTTTGGAGC	CGCTGTGAC	ACACACAGAA	AACTTTGTGC	490
10	CTACTAAAAA	TACAAAATTA	CGTGGGATG	GTGGCAGATG	CGTGAATATC	CAGCTACTGT	CGACGGTCAG	560
	CGAGGATGAC	CGCTTGACCC	CAGAGGTTGG	AGTTTGGGCT	GGGCGGGGAT	TGGCGCTGCT	GACTCTAGCC	630
	TGGGTTAAAC	GAGTGAAGCC	CTGTCTCAAG	AAAAAAGAAA	AGTTTGAATA	ACTTAAAGAT	AAAGCTTAAT	700
	GATGACCTTT	AAATGACTAT	GAAGGAGAT	GCACATATAT	ACAAAAGATC	ACCTAAATTA	AAATTTATAT	770
15	AGATGAGGAG	CGAGATATA	TGAAGTGA	AGATATATAT	ACAAAAGATC	ACCTAAATTA	AAATTTATAT	840
	TTTGAAGAG	ATAAACAAAA	TGACAGAAC	TTGGCCAGCA	CTAAGAAAAA	AGGAAGATAG	ACCTAAATTA	910
	ATTAAGAGAG	AGATGAGAAA	AGAGACATA	CAAGTATATC	CAAGAAATAT	CAAGGATATC	CTAGAGGCTA	980
	CTATGAGCA	CTGTACATA	ATAAATTTGA	AAAGCTTGA	AAATATATAT	ATCTCTATAT	TGCTATATAT	1050
	CTACAGATAT	TGACATGTA	AGATATGTA	AGGCTAAGCA	CACTATATAT	AAATATATAT	TTAAAGGCTA	1120
20	AAATTAAGAT	CTCTGAGCA	AGAGAGGCC	AGGACCCAT	GGCTTCTGCT	CTGGTTTAT	CCATATATAT	1190
	AAACAGATAT	GAATTCCTAT	CTCTGAGCA	CTATCTGTA	AAATATATAT	AAAGATATAT	CCAAATATAT	1260
	TTTACATGCT	CAATATATAT	CTGATGCTA	AAACGATAT	AAACGATAT	AAACGATAT	AAACGATAT	1330
	CAGAGAGGAA	GAAGATATAT	GGGCTTCTG	CTGATGCTA	AAATATATAT	AAATATATAT	AAATATATAT	1400
	GCACAGGAA	TTAAGACATA	CTTCTGAGAG	ATCATATAT	GTGATCAAGT	GGGATTTAT	CCAGGATGCT	1470
25	AGAGATGCT	CAACATATAT	AAATCACTA	ATGATATAT	TCATCCACAC	AAATATATAT	ACAAATATAT	1540
	TTTATATAT	TCATCTATAT	CAAGAGAGG	ATTTGATAT	ATCTGACAT	CTTCTATAT	AAACGCTTAT	1610
	AGGCAAGAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGCTCTACAT	TGCTCTATAT	CGCTCTGCT	1680
	CTACAGGAAA	CTTTTATAT	AAATGAGCA	GGGATTTAT	CTATCTGCT	CTATCTGCT	GAGGATGCT	1750
30	CTGAGGATGCT	GAGATATAT	TAACTATAT	AGGCTATAT	TGCTCTGCT	CTATCTGCT	TAGTCTGCT	1820
	CTGAGGATGCT	CAACAGAGCA	AGGCTATAT	AGGCTATAT	TGCTCTGCT	CTATCTGCT	TAGTCTGCT	1890
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	1960
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2030
35	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2100
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2170
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2240
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2310
40	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2380
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2450
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2520
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2590
45	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2660
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2730
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2800
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2870
50	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	2940
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3010
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3080
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3150
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3220
55	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3290
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3360
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3430
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3500
60	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3570
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3640
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3710
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3780
65	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3850
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3920
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	3990
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4060
70	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4130
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4200
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4270
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4340
75	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4410
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4480
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4550
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4620
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4690
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4760
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4830
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4900
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	4970
	AGGCTATAT	GGGATATAT	CTTCTGAGG	CGAGGATAT	GGGATATAT	GGGATATAT	GGGATATAT	5040

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5	TCGACGGGAG AGGCGTCGATG ACCGAGGAGC AGGAAAGCTC GGATGGGAGG GGGCGATGAG AAGGCTGCTT 5180
	CGTTGGCTGAG CAGCGCATGA AGTGCCTTAT TTATCGCTTT GCAAGGNTTG CTCTGGATAC CATCTGGAAA 5250
	AGGGGGCGAG CGGCAATGGA AGGATATGAA AGGCTCTCTG TCAAGCCGAG GCGACGAGCT ATGGCGGCCA 5320
	CGCGGGCGTG TCGCAGAGGG AGGAGGATAG AGGCACTCGG AAGTATGAGT TAAATCTTCT TTTCACCTCG 5390
	AGGATGAGCC AAGGTCTATT CTGAGGAGAC CTGAGGCTAG GTGCTGCTTT TAAAGACAA AGTGGTGA 5460
	GCACCTCTCT CAAAGGAAA CCGAGGCCG GCTCTGCGGT CATTTAGGCT TTCTGCTCTG CCCTCTCTTG 5530
	CGCTCGCGGT TTCTGATCGG CACAGATGTA CCGGCGTGGA GCTTCTCCGA CCGCTGCTG AGGACAGCTT 5600
	TCGCAAGAGGC TCCACAGAGC CCGCGCTGG AGAGAGAGGT CTTAATAACA AACTTGGAGT 5670
	TGGCTGGGGG CGGACAGCGA CCGGCGGATT GAAGGACTTA ATTGATGAG TAAATTCAG CTCTTCCACT 5740
10	CGAATGGAT TGGATTTTA TCTTAATAT TCTTATAT TGTCAATA AACTTACGAT CCGACCAAT 5810
	CCAAAGGCGT AAACAGGAAA CTGAGCTATG TTGCGCAAG TCCAGAGGACT TGAATACCAT GTTCCAGGCG 5880
	ATTTTCTGCC CTAAGTATCT TTTATGGTGT TTCAATAGT TGTCTTAGGT GCAAGGAAA GTACACGAG 5950
	AMGAGCGCTG CGCGCAGGCG TATGAGGACG GCAAGGCGAC CGGGGAGGTA GTGCTGCGCG TGGAGGAGCT 6020
	ACACAGCAGC CAGCTACGCT GCGCTCTGCT TGGCTCCGA TGGCGACAG CGAGGCGGCG CAGCTGCTGT 6090
15	GTGACTCGAG ACCGATACCT GCTCTCTGCG GCGCACCGAC AC7AAGCCAG GAAGTCTGAG AGCTCTGAC 6160
	CGGTGGCAAG GAACATGACC CTTCGCTCGT TCGTCTCGT GGTGGGTCAA GGGTATGAAA GTGGGTGAGA 6230
	GGAAATGGCC ATGTAAATTA CAGAGCTCTG CTGATGGGGA CCGTCTCTCT CATGATATT CATCTTACG 6300
	CCCAAGAGCT GAATGATCC AGCAACTTCT TCGGAGTGTA CAGGCTGTA CAAGCTCTGA CAATACAGC 6370
	ACTCTTTAC TGGGACACA GAGCAGGCG GCTCTCTGCG GCGCACCGAC AC7AAGCCAG GAAGTCTGAG 6440
20	GCTTTACGCG ACCAGCGCTG GGTGACAACT GCGGCTGAG AGTCTGTTTC TCTAGACTAG TAGACCTGTC 6510
	CAGGCACTCG CCGGATTTCT AGGCGCTGGT TCGTCTCTG TCGAGGCTCT CAGCTCTGCT GAGACTCAGC 6580
	CTGGGTGGCG ACAGTGGGCG CCGTCTCTCA GCGTCTCTG CCGGCTGAGG GCGTCTGCT CTCCAGCGCG 6650
	TCTCTAACG CTGGGTGGCG CCGTCTCTCA GCGTCTCTG TCGTCTCTG CAGCTCTGCT CAGTCTGCT 6720
	TCGTACGCTG CAGGCTCTCT CCGTCACTG GGTGCTGCTG TCTCTTCCGA ACCTACACAT CCGTGAAGG 6790
25	GAGGAGATTC TGGCGCTCCC AGACTGCTC CTCTGAGCTT GAGCTGAGCT CGGCGGCCCG GATGCAAGTT 6860
	CTCTGGCTCG GCGTCTGACG TGACTCTCAT TCGCAGCGCG TCGCGCTCTC CTGTACATCT CGGGGCGCT 6930
	CGGCTGTGTT CTCTGCTTCT TGTGCTCTCT TCGACGCTCA CCGTGTGCTG CTCTGCTCG CTGGAGCTG 7000
	GGGCTTTTA TGGCTATAG AGGCGGCTCT GGTGAGCAG GCGTCTCTCA GAAGTACCAA CATTTGGGTG 7070
	TGAAAGTAG AGTCTCTCT CTCACCTAGG TCGACGGGCA CAGCGCTGGG GATGAGGCGT CCGGCAAGCA 7140
30	CGCGCGCTTC TCGCGCAGC ACTTCTCTCG CTGAGACACA GAGTGGGCAAT TTCCACAGCG 7210
	ACTAAGACTC CTCTTGGCA AGAGCAGCAG ATTGGGAGC CTGGGATTTT GCGCCACAGC ACTGGGAAAT 7280
	CGCTGACTCA CAGACATGAG CCGTCACTG CCGTCACTG CCGTCTCTCT CTGTTTAT TTAATGCTA 7350
	CALAGCAGGA AATCCCTCG TAAATGTCT TTTAACAGC TGGTAAJAA AACGGGTGCA TCGCGAGCT 7420
	GGACAGTCTC TCACAGTGA GAGGACATG AGCTTTATA AGCTCTCAGG CATCTCAAAG GAATTAAGCT 7490
35	GAGTGAJAA TGGCACTGCG ATGGGATAG TACGACATCT CAGCAJAAAG AAGATATCT AGCGCATAGG 7560
	AGGCGAGTGT TATGGGGGCT TAGGCGCTCT GCTGGGAGCT ACTGACAGA ACTGACAGA CTCTTACTA 7630
	GGAACTGGGA GCGTGTGCGA TCTTTGGCAT GCGCCAGTGT CTCTGGGACG ATAATGCTCT AGAGATGCG 7700
	AGCTCTGAT TCGCCAAJAG CTGTGAGCAT AACCGGCCCG CCGCCAGGCG CTTTCCAGGT GTGATCTCG 7770
40	TGAGGAGGCT GAGGCTGCGG ATGCTTGGGG ACTGACTGCA GCGCCGAAA GTAACTAGCG GGTCTGGGA 7840
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	GTCTCTCGG GCAAGGCGG GCGAGCGCTG GCTGAGTGT TTTAGTATT TATTTTAT TACTATTCT 8360
	CTGACAGCA GTTATGCTCT TGTGCGCAG GCTGAGTGT AGCGGATGA AGCGGATGA CTGCAACTC 8430
	CGCTCTCGTG GTTCAAGCAA TTCTCTGCG CAGCTCTCGG AGCTCTGCG GATTTCAGCG GTCTCAAGC 8500
50	ACACCGGCGT AATTGTGAT TTTTATGAA TAGGGGCTCT CAGCATGTCT CAGCATGTCT TCTGAAATC 8570
	CTGACCTG GTATGCGCT CAGCTCAAGT GCGTCAAGT GCGTCAAGT GCGTCAAGT CAGCTCAAGT 8640
	GGGCTATTA ACCATTTTAA AGCTCTCTG GCGTCAAGT ACACCGCTG GTAAGGAGT CATGAGCTG 8710
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	CGCTCTGTGA CATATTCACA GTTCTGTTGA TCGCATGTGA TCGCATGTGA TCGCATGTGA TCGCATGTGA 8850
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55	AGTCTGGA CTCTCTCTA ATCTCAAGT CTATCTCTCT CAGTCTCTCT ACTGAGTGT GCGTCAAGT 8990
	CGCTCTCTCT ACTGGATGT AGCGCTCTCT CTATCTCTCT CAGGCGGCG AGGAGTCTCT CTAATCTCT 9060
	TGAGGAGGAG AATGATATC TTGTAATTT CTATCTCTCT ACTGAGTGT CAGTCTCTCT ACTGAGTGT 9130
	CTTGTCTTCT TTGAGAGGCG GTTCTCTCT TGTCTCTCA TGTCTCTCT ACTGAGTGT GCGTCAAGT 9200
	GTGATCTGA CTCTCTCTCT GATGATGAG GTTCTCTCT TGTCTCTCT ACTGAGTGT GCGTCAAGT 9270
60	CGGACCGCG CCGCATCTCT CAGCTAACT TTTTATTT TGTCTCTCT TGTCTCTCT ACTGAGTGT 9340
	ATGTTGGGCA GCGTGTCTCT GAAGCTCTGA CCGTCTCTCT CAGATTTAG TGTCTCTCT TGTCTCTCT 9410
	GATTCAGGCT GATGAGCGAC ATGCGGCTCT CAGATTTAG TGTCTCTCT TGTCTCTCT ACTGAGTGT 9480
	GTATCTCAG CCGCTCAACT GTTGTGCTGT TTTAGGCA TGTCTCTCT TGTCTCTCT ACTGAGTGT 9550
	CCTCTGATG TGTCTCTCT GATGATGAG GTTCTCTCT TGTCTCTCT TGTCTCTCT ACTGAGTGT 9620
65	ATACTGGGCT GCTCTCTG GATCAAGCAT TCTCTCTCT TGTCTCTCT TGTCTCTCT ACTGAGTGT 9690
	GGTGTAAAT ACTCCAGCAT AATCTCTCTG TGTCTCTCT TGTCTCTCT TGTCTCTCT ACTGAGTGT 9760
	ATTGTTGCTT CTCTCAGAG AACAGTGTGA AGTCAAGCT TACTTTGT TGGAGCAAT TTTGCAAGC 9830
	CGGCTCTCT CTCTGAGCA GAGCAACTCT AGTCAAGCT TACTTTGT TGGAGCAAT TTTGCAAGC 9900
70	GGATTTCTAG AGGAGCGAC TGTAACTCTA AGTATTTCA AGTCAAGCT AGTCAAGCT AGTCAAGCT 9970
	CGGAGGAGG GCGCTGAGCG CTGTTAAAT GGTATGCTCA TAAATAAAG AATTCTCTCT GCGAGTCT 10040
	GAAATGAGGA AGGCTTACAT TTAAGTCTCT GTTGTGAG ACTTTCACT TGTCTCTCT CAGTAAAG 10110
	ATGCTTGACA GCGCTCTGGA GAGCAGAGG TTTCTGCGG CTTAATCTT AACTCTGAG AACCGGAGT 10180
	CGGATGTCT GGAAGTCTCT CAGCTCAAGT GGTCTCTCT GGTCTCTCT GGTCTCTCT GGTCTCTCT 10250
	CGGCTCTCT CTACTCTCT GCGTCAAGT GCGGCTCTCT AGCTCTCTCT TCGGAGGCT CAGTCTCTCT 10320
75	CGGCTCTCT CAGGCTCTCT CCGCAGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT 10390
	ACAGATGCT GCGGCGCGAG GTCAAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT 10460
	CGGCTCTCT CAGGCTCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT 10530
	TTGCTCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT GTGAGGCTCT 10600

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	CCCAAGTCGC	GGGAGAGTGT	TGCAGGGAGG	CACCTCCGGA	GGTCCGCGDT	GCCTCCGCGA	GGAGCAATGC	10640
	GTCTCCGGGT	TGCTCCCGAG	DDGCGTCAC	GGCTCGTGGT	GCTCCCTCTC	AGCTCCGCGA	TTCGTGGTGC	10710
	CCGGAGCGCG	AGCCCGCCGC	TCCGAGCTGT	CAGCGAGCGC	TGGGTCTCCG	GATCAGGCGA	GCGGCAAGAG	10780
	GGTCCGGCCA	CGCACTCTGT	CCCAAGGCGT	CGCATATCTG	GGCTCCCTCT	CGAGTATACC	AGCGAGTAC	10850
5	GCAGATTCGA	CTCTCTCTCG	CTGGGCGCT	CGCAGGCTGT	CTGCGAGCGT	GGGAGAGGCG	CGCAGGCGCT	10920
	CCGCGGAGAG	CGCGCGCCAG	AGCCCGGGGT	CCGCGCGGAG	CAGCTTGGCT	GGTGGGCGCA	GGCGCGGCTC	10990
	CCAGTGCATT	CCCGGGGACA	GACGCGCCAG	ACCGCTCTCC	CCAGTGGGCT	GAGGAGCTGC	GACCGCGGGC	11060
	GGGATCGCTG	CCCTCTCACC	TTCGACCTGC	GGCTGTGTGG	GGCGAGACCG	GGCGCTCTGC	GGAGCTCTGC	11130
	GGGTCGCGCG	CGACGCGCGT	TCCGAGCGCT	CGGAGCGTGT	CGCTCTCTCT	TCCGCGCGCG	GGCTCTCTGC	11200
10	GGGTCGCGCG	AGTTTCAAGC	AGGCTGTGCT	CTCTGTCGCG	ACGTTGGGAG	CGCTGCGCGC	GGCCACCGCC	11270
	TGGATGCGCG	GGCTGTCCCG	CTGGCGAGCG	TGTGGCTGCC	TGC TGC GCGC	CCACTTACGC	GAGGTGCTGC	11340
	TTCTCGCGAC	CTTGTGTGCG	GGCTGTGGGG	CCGAGGCTGT	GGGCTGGGTC	CGCGCGCGCG	ACCGCGCGCG	11410
	TCTTCCGCGG	CGCGCGCCAG	AGTCTCTGGT	CTTGTGTGCG	TGGGAGCGCG	GGCGCGCGCG	GGCGCGCGCG	11480
	DACA TGTGGA	CGGAGCGCGA	GGGAGCTCAG	GGGCTCTCCG	CGCGAGGTGT	CTTGTCTGGA	GAGGCTGTGT	11550
15	CGCGAGCTGT	TGCAGAGGCT	GTGGCGAGCG	GGCGCGAAGA	AGTGTCTGCC	CTTGTCTGCC	GGCTGTGTGT	11620
	ACCGGCGCGG	GGGCGCGCGC	CGCGAGGCGT	TCCAGCAGCG	GGTGGCGAGG	TAGCTTGGCA	ACAGGCTGTG	11690
	CGAGCACTGT	GGGCGCGAGG	GGGCGTGTGG	GGCTGTCTGT	CGCGCGCGCG	CGCGAGAGAG	CTTGTGTGTG	11760
	CTGTCTGCGC	CTTGTGTGCT	CTTGTGTGCT	GTGGCTTCCA	GTGGCTTCCA	CAGAGTGTGC	AGCGCGCGCG	11830
20	TGTACAGGCT	GGGCGCGCGC	ACTCAGCGCG	GGCGCGCGCG	ACAGGTAAGT	GGACCGCGGA	GGCTGTGTGT	11900
	GTGAGACAGG	GGCTGGAGCG	ATAGGCTGAG	GGAGCGCGCG	GTGCGCTGCG	GGCTGTGTGT	GGCGCGCGCG	11970
	AGGAGCGCGG	GGGCGCGCGC	CAGCGAGAGT	GTGCGCTGCG	CGAGAGCGCG	CAGGCGCGCG	GGCTGTGTGT	12040
	AGCGCGAGCG	GAGCGCGCGT	GGGCGAGGCG	CTGCGCGAGG	ACCGCGAGG	CGAGTGTGTG	CGAGTGTGTG	12110
	TGTGTTCTGT	GTGCTGTGAG	CTGCGAGAGG	CGCGAGAGGA	CGCACTGTGT	TGAGAGGCTGT	GGCTGTGTGT	12180
25	ACCGGCGCGT	CGGCGCGCGC	GTGTGGCGCG	CAGCACCGCG	CGGCGCGCGC	ATCCAGCTGT	GGCGCGCGCG	12250
	CTGCTCGGGA	GGGCGCGTGT	CCCGCGGTGT	CAGGAGCTGT	CTTACTCTGT	GGGCGCGCGC	GGGCGCGCGC	12320
	GGGAGCGAGT	GGGCGCGCGC	TGCTACTCAG	CTTGTGTGAG	CGGAGCGCGC	TGAGGCGCGC	GAGGCGCGCG	12390
	GAGGAGCTGT	GTGCGCGTGT	CAGGCGCGCG	ATGCGCGAGG	CTGCGCGCGC	GTGCGCGCGC	GGCGCGCGCG	12460
30	CTACTGCGCA	AATGCGCGCG	CTGTTCTGCG	GGTCAAGCGG	CGAGCGCGCG	CGAGGCGCGC	CGGAGCGCGC	12530
	CGGCGCGTGT	TGCGCGCGCG	CGGAGGAGAG	CAGGAGCGCG	CGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	12600
	ACAGCGCGCG	GTGCGCGCGC	TAGCGTGTGT	GTGCGCGCGC	CGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	12670
	GGGCTCTGCG	CAGGAGCGCG	GGGCGTGTGT	CAGGAGCGCG	AGAGGCTGTA	CTGCGCGCGC	GAGGAGCGCG	12740
	AGGCTCTGCG	TGCGAGGCTGT	GAGGCGCGCG	ATGAGGCGCG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	12810
35	GTGAGGAGGT	GGTGGCGCGC	GAGGCGCGCG	CGGCGCGCGC	TGAGTGTGTG	AGGCGCGCGC	AGGCGCGCGC	12880
	GGGAGCGCGT	GTGCGCGCGC	TGCTGTGTGT	GTGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	12950
	TGCGAGCTGT	GATCTGTGCG	CTTGTCTGCG	CTTGTCTGCG	CTTGTCTGCG	CTTGTCTGCG	CTTGTCTGCG	13020
	CTGTTGAGT	GAGCGCGCGC	TTCAGGCGCG	CGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13090
	TGAGCGCGCG	TGCGCGCGCG	TGCGAGGAGG	TGCTGTGAGG	CAGGAGCGCG	GTGCGCGCGC	GGGCGCGCGC	13160
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	GGTGTGAGG	TAGGCGCGCG	GAGGCGCGCG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13300
	GTGTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13370
	TCAGCGCGCG	TGCGAGGCTGT	GAGGCGCGCG	TGAGGAGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13440
	AAATAGGCTGT	GGGCGCGCGC	TGCGCGCGCG	TGAGGAGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13510
45	TGAGCGCGCG	AGGCGCGCGC	TGCGCGCGCG	TGAGGAGCGC	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13580
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	AGGCTGTGCG	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13720
	AGGCGAGGCT	AGGCGAGGCT	GAGGAGGAGG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13790
50	CTGTTGCGCG	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13860
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	13930
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14000
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14070
55	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14140
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	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14280
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60	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14490
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14560
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	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14700
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14770
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65	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14910
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	14980
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70	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	15260
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	15330
	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	15400
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	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	15540
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75	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	15750
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	AGGCGAGGCT	AGGCGAGGCT	CTGTTGCGAG	TGTTTGTGAG	GGGCGCGCGC	GGGCGCGCGC	GGGCGCGCGC	16030

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	24	TATTCCTGGA	TATTTTAAAG	CAGTGAGGTA	TTTGACACCT	GTGTAATGTC	AAGATATGTA	GAGTATCAAG	16160
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		ACCAATATTT	TGAGTCTTGC	GGAGCCTTGG	TTTGATGATC	AGGTGTGATC	TGTTTTCGCA	AGGTGTGATC	16240
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5		AAGCTGCTGT	CTGCTCTGAT	ATGATGAGAC	TTCCAGAGAG	GAGGCGATAG	TGCTTCACCT	GGGAGATGAG	16380
		TCCTGTCAT	TCCTGTCAT	TGCTGAGATC	TATGAGAGGC	ATGTTGAGTC	CGATGACAT	GCTGATGATC	16460
		TGCTGTCAT	GATGAGTAA	TGCTTTGAGAG	ACTCTATGTC	CTCTAGTAT	GATGATGATC	TTTTTTTAA	16520
		TGCTGCTTA	TACTGCGACA	CTGCGCTTCT	TGTGATTAAG	ATTTTCTGTC	TGCTGCTGTC	TGCTGCTGTC	16590
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10		AGTGGGTGGA	TACACGCTGA	GTGGAACCTT	TAGCTGCTGC	CTGTGAGGCT	CTCTTCACCT	GAGCTCTGTC	16730
		AGTGGGTGGA	ACTGCGACCA	CCGACCGCTA	CAGCTGAGCT	ATTTTAAAT	TTTTTTCGCA	GAGAGGCTGC	16800
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		CTGAATATCA	GGCATGAGCG	ACCATGTCGT	GGGTAAATTT	CACATCTTTT	ATATCTTAT	AGTGTGGGTA	16940
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		ATTTGCTGTC	TTTTGCTTGT	TTTTATGAGA	CAGCTCTACT	CTGTGACCA	GGTGGAGTGT	TAAATGGACA	17290
		ATTTGCTGCTG	ACTGCAACTC	CTGCTCTGCT	CTGTTGACCA	GTTCCTCATC	CTGACATCTA	TGATGATGTC	17360
20		GATATGAGG	CGGCGACAC	CAGGCTGGGG	TAAATTTTGT	ATTTTATGTA	GAGATAGGCT	TTTCACTATG	17430
		TGCGCAGGCT	GGCTCAAAAC	TCTTGACCTC	AAGTGATCTG	CCGCGCTTGG	CTGCTCCACG	TGCTGGGATG	17500
		ACAGGTGGCA	CGACCGCTGC	CGGCGATACC	TGATCTGTTT	AAATGAGAT	CTGACCAATG	GCTTACCTGT	17570
		TGCTGGGCAA	TAAAGAGGCT	AGTGTATTTT	AGCTGTGACC	ATGCTGAGCT	CTGTTGATGT	TTTTTCCCTG	17640
		TGACTGATG	GTATGTGAGG	CATGTGACG	CCCCGACAG	CTAGGATCTA	TATATATGTC	TGCTGCTGTC	17710
25		GGAGTTTCT	GGAGTTTCTG	CCCCGCGCTG	CTTTTCTCTC	TTTGTGCTCC	GCTGCTCTCT	TGCTTCCAGC	17780
		CGGCTGCTG	GGGCTGCTG	CTCTGCTGCT	TGCTGTGCTG	TTCTGCTGTC	TATTTGCTG	TAAACCCGAC	17850
		CTTTACTGCT	GGTGGCTGCT	AGGCGATCTA	GGGAGCTGCT	CTTATGATCT	AGCATGTGAG	17920	
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35		TGCTGGGCA	ACAGGCTGAT	CAGCTGAGGC	ATGCTGATTA	TTTTTAAAT	CTTGGCTGCT	GGGCTGGCTG	18410
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		CTCTGGGCA	ATGCTGATCA	CTTGGGAGGC	CTAAAGGCTG	AAAAATATG	TGCTGGGCTG	GGGCTGGCTG	18550
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		TGCTGGGCA	ATGCTGATCA	CTTGGGAGGC	CTAAAGGCTG	AAAAATATG	TGCTGGGCTG	GGGCTGGCTG	18690
40		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	18760
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		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	18970
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45		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	19110
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		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	19740
		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	19810
		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	19880
		GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	GGGCTGCTG	19950
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Le A 32 805-Foreign Countries

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	CAGGAGGCTCT	CGGAGGCTCT	GGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	30170
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	TGAGGCTCT	CTTCAAGAGC	ATGCGGCGGA	AGGAGGCTCT	CTGTCACCT	GGCTCTGAT	CCGAGAGGCT	30310
	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGAGGCTCT	AGGAGGCTCT	AGGAGGCTCT	AGGAGGCTCT	30380
	CAGGAGGCTCT	CGGAGGCTCT	GGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	CGGAGGCTCT	30450
	GGGCTGTGCT	CAGGAGGCTCT	AGGAGGCTCT	GTGCTGTGCT				

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Contig 2:

	TTGGGATG	GTTCATGCT	GTGGGATAGG	TGGGATCTG	TGGGATTTGGT	TTTTATGAGT	GGGGTAACAC	70
	AGGTTCTCAAG	CGGAGCTTTC	TTGCTGTAGT	GGGTCGACG	GTGCTGCAC	AGCTTTATGT	AGGAGACCAT	140
5	ATTCTTCCTT	GACATATGGT	GGGGTTTATA	TGATGTCAGG	GGGTGGAGAG	CTCCGCTGTT	GTCTCGTGT	210
	CTGCTTCTTC	CAGCTGTGGG	TGTTGGTGGT	CTCTCTTTGG	TGTTGGGCGG	GTGGGAGAGG	CTTCCAGGCG	280
	CTCTTGTTGT	CATTGGGCTG	GATGNGGCG	TGGCTGCTGT	CTCTCTCTGG	AATTCGCGTG	CGATTGAGG	350
	GGCTTCTTTC	TTCTCTTT	TTCTCTTT	TTTTTTTTTT	TGATAACAGA	GGTCTGCTCT	TTTGTGGCCA	420
	GGCTGGAGTG	GTTTGGGCTG	ATCTTGGGCT	ACTGCAAGCT	GGGCTTCTCT	AGTTCAACGA	ATCTCTCTTC	490
	AGACGAGCTC	CAMGTAGCTG	GAATTATAGG	GGGACACAG	CATGCTGACT	AATTTTGTGA	ATTTTAATAG	560
10	AGACGAGGTT	TTGCTATGTT	GGGCAAGGCT	GTCTGAGACT	CTGAGCTTCA	GGATGATCTC	GCACCTCGCG	630
	CTCCCAAGT	GTGGGGATGA	CAGGTGGA	GGGCGGCT	GGGCGAGAG	TCCTTCTCT	CAGTCTGGT	700
	GAGATCTGCA	GGGATAGCTG	CTGCAAGCT	TGGTCTGAC	AMCTCCGGT	TTCTCTCTCT	AGGCTTGCTG	770
	AGGGGCTTTT	CCATTCTATG	ACTCTCTTCA	CAGAGAGTT	TCAAGCTGCG	TGATTTCCCG	GCTGTTTCTT	840
	CGCTAATTTG	TGTCGCTGT	TATGAGATGT	CTCTCTTCCA	TTTCTTTTAG	GCTTTTGTGA	TGTGTTTGT	910
	CTCCGCTCT	TGAGAGTAA	GTTCGATTA	TGATGTTTG	ACTTTCTTTT	TTTAAACAG	CATCTTGAGT	980
	TGGGCTTTG	CTCTTAAGCG	AGGATACCGG	AGGCGCTGG	CTGTGGAGTG	GGACCGCTGT	GGGGCTCTT	1050
	AGGACCTGGG	GGACACCGGG	GAGGCTAGCT	GGGATGTTGG	GAGCGAGCT	TCCCGCTGTA	GGCCCGGCTC	1120
	CTCCAGATCA	CGAGTGACAT	CGGGTGCTCA	GAGCGCGACA	CAGGCTACTC	AGACACTGTG	GTGAGAGGGG	1190
20	TCTAGA TTCT	GTGCTCTTGA	TGGGAATCTA	ATGCTGATGG	ATGCTGATGG	GGACCGCTTG	CTCCCAAAAC	1260
	CATCGCTTC	CCGACGCTG	TGCTGTGGA	AAATGTCTT	CCGCAAAAG	ATCTCTCTCT	ACCAAAATAG	1330
	TTGGGGGCCC	TGTGCTAAAG	ACCTGCTTCA	CGAGGCTCTC	GTCACTGTTG	ATATATTTGG	TTTCTGCTGT	1400
	TGAGTCCAGA	ATAATTAACG	ATTCTGTCTA	TGCTTTCCCG	CGACCTCAGA	CCCATGGGCT	ATTTGTGGGG	1470
	TGTTGGTGTG	CTCTGGGCTT	GGGAGGGGTT	CAGGCGCCAT	GTACTTCTCT	GTACTGCTCT	TCCAGGTTGT	1540
	TTCTCAAGGT	TGATGCTGAC	TGCTATGCT	TTTATGGCAG	GGGCTGGGCG	CGAGCTCTG	GGGCGTGGGG	1610
25	AACATGCTGA	AGCAACAGGT	CAGGCTGGCG	GCTCTTTGAT	GGCTCAAGG	CTCGAGCTGAG	GGGCTTCCCG	1680
	TGTTAGTGTG	TGTCACGTGT	GTCTGCACAT	CTGTCTTTGG	GGACGACGGG	GCTTAGGACAG	TCCGCTAGTA	1750
	AATGACAGCG	CTCTGGGGGG	AGTCTGACAG	ATAGAGGGGT	GGGGTGGGCG	TTCTCTTCCG	GCTGCTTCAAG	1820
	ATCTTCTTCC	CTCTGGTGGT	GTCTGCTGCT	CGATCTCTCT	CATGCTTCTG	CATGCTTCTG	GGGCTGCTG	1890
	CGGGGAGCT	GGATGCTCACT	TGTGCGACGT	GACTTGTGAT	GGCAGTGGGT	CAGCGGGGCT	TGATGTTGGG	1960
	TGACTGTGGA	TGGGGGTGCG	TACAGCGGCT	CTGATGTTG	GTGACTGTGG	ATGGGGGGTG	TGGGGTCTGA	2030
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GTACTGTGAG	ATGGCGGGTG	GGGGGTCTGA	2100
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2170
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2240
35	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2310
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2380
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2450
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2520
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2590
40	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2660
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2730
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	2800
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45	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3010
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	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3220
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50	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3360
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3430
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55	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3710
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3780
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3850
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	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	3990
60	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4060
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4130
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4200
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65	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4410
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	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4550
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	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4690
70	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4760
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4830
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	4900
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	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	5040
75	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	5110
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	5180
	TGTGTGACT	GTGGATGGCG	GTGTGTGGGT	CTGATGTTGG	GACTGTGAT	GGGCTGGTGT	GGGCTGGTGT	5250

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	GAAGCTCTTC	GGCGACGAT	TGAGGACCTG	AAGTACATAC	TGACGCTGGG	CAGCGGCGTG	TGACAGCTCT	5320
	CTCTCTCTCT	CTCGCGATAC	TAAGGACCTG	TGAGGACCTG	TCACTCTCTG	CGCTGGGCTG	TGACGCGCTG	5340
	GGCGCGCGGG	CTGCTCTCTG	CTGTGCTACT	AGTATTCCTG	TGGAAAGATG	CGGTGTGACC	GTTGATATG	5460
	CTCTCTCTCT	GGGCGCTCTG	CTGTGCTACT	GGCGATGCGG	TGCGGAGAGC	TGCGCTCGAT	GACGACCTAT	5480
	GGCGCGACCA	CTGCGCGTGG	TGAGGACGAA	CTGCTCTGTT	CCGATCATCG	CTGCTCTGGAT	TTTGAATATG	5500
	CGACGACG	TGCGCGGATG	TGAGGACGAA	CTGCTCTGTT	CGGCGGCG	ACGCTGGGATG	CTGCGGATAT	5520
	AATTGCTGCG	CACTCAAGGG	GTATCTCCGA	CTGCGTGGGA	TGCGGTGGGA	ACGCTGGGATG	CTGCTCTCTG	5540
	GATGCGCTCG	ACGGGACATAA	CGCTGTGCGA	ACGCTCTGGA	AGGCTTTTAT	TAAATATATG	ACTATTAAAT	5560
	ATTGCTGATAT	AGTAATCAAT	TAAATGATAT	AGCAATATAT	ATATTTATAT	AGTAATATAT	AGAAATATAT	5580
	ACAGTACAGCA	ACGTTTGTGG	AAATACATAA	TTGCACTATG	AAATTTTCTG	AAATTTTCTG	CGAGAGAGAG	5600
	CGGCGGCGCG	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	5620
	ACGCGCGGCG	CTGCTCTCTG	CTGCGGCTCT	TTTAAATGAT	GATCACTGCA	CTGACGCTCG	AGGCTGTGCG	5640
	GGGCTTTTGG	GAATGTGCGG	TGATGATCTG	GTGCTCTCTG	CTGCGAGAGC	AGGAGTGCGT	TGCTGTCTCT	5660
	CTGCGGCTCT	CAGCGGCGCA	GGGCGGAGCG	CTGATGCTCG	ATGCTGTGCT	ATGCTGTGCT	CGTAATATAT	5680
	CTGCGGCTCT	ACACGCTGTG	GGGAGAAATG	GGGAGAAATG	TAGATGATG	GGGAGAAATG	CTGCGGCTCT	5700
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	GGGAGAAATG	GGGAGAAATG	CTGCTTTTCT	TTCTCTCTCT	5720
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	TGCAAGCTCT	GGCTCTCGGG	CTGCGGCTCT	CTGCTGTGCT	CAGGCTCTCG	AGGAGCTCTG	ATTACAGCGA	5760
	CCGCGCTCTG	GGGCTGTGCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	5780
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7400
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7440
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7480
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7500
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7520
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7540
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7640
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7700
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7720
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7740
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7760
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7780
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7800
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7820
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7860
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7880
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7900
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	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	7980
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	8000
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	8020
	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	CTGCGGCTCT	8040
	CTGCGGCTCT	CTGCGG						

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5	STGGGGATCT	CGCTGCACCT	CGGCTCTCTG	TGGGCACTTG	CGTCCACTTG	CTCTCTCTGG	TGCTTCTCTG	16240
	CTCTGGCCAG	CGCTGGGGGG	AGGCAAGATG	CACAGGATCT	TGACTCTGCC	AGGGTCTGTC	CGAGCTGTCG	16310
	GGTGGAGGCC	AGGCGCGATT	TGACTGGGAA	GAGGGGATAG	TGCTTGTCAC	AATGTCTCTC	TCTCTCTCTG	16380
	CATCTGGAAT	GATGATAAAG	CAAAAATGAA	AAACTTAAAA	TCCCAAGAGG	GTCTTCTAGC	TTTCTGACTC	16450
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	CTGACCGGGG	GCCTCACTCT	GGAACTCTTG	GGCTTTAGGG	GCAGGGAATG	TCTGACTCTT	TCATGTGCTC	16660
	TGCTGCTGTT	GCAGAGTTCT	GTTCCTCTGG	CTGTATGAC	AGACATCTGT	CGCATCTCTT	GGGATGTGGT	16730
	AGAGGCGAGT	GTGGGCCGAG	GTGTCCTCAG	TGCTGCTGTT	CAGTGGCTGT	GGAGCTATCT	GGAGGCTATC	16800
	CGAGGCGAG	AGGCGATGAG	GTGTAAGAGA	TGTTTATGAG	GGCTTTAGG	AGAGAGAGCT	GGGAAGTGTG	16870
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	CAGGATGCGA	CACCTTTATC	ACAGAGGGAA	GGGCAACTCT	GTGAGGGGCA	CAGGCGAGCT	TTCTGCTCTG	17150
	AGTCAGAGCG	GTGGGTGGCA	CAGGCTCTGG	GGCTTCAGCA	AMGGGCACTG	GGGCACTTCA	GGGCTGGGCTC	17220
	TCAGACTGAA	CAGGCTGCGC	GAGGCACTGG	GAGCTGAATG	CGAGAGGGCG	GAGGCGCTCG	CCCCATGAGT	17290
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	TGAATGTGAG	TCGTCTGTAG	TGTGTGAAGC	CGAGGCTGCG	GGGCAACTCT	GGTGTCTGCT	ATACAGTGTG	17430
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	GTGCTGTGAG	TCGTCTGTAA	GTCTCTTCTC	TCCTTTGCGG	AAAGCTCTGG	GGTGTCTGCT	ATACAGTGTG	17710
	CATCTGAGAG	TGGAGTGTCT	TGACACTCTG	GTTCACCTCG	GGGCTCACTG	GGCTGTCTGT	GGGCTGCTCT	17780
	GGGCTGTGAT	GAGTGTAGAG	GAGTTPCTCG	AGGTCAAAAC	TCTGTGGAAA	CTCCAGAGGC	CATGTGACTC	17850
	GGCACTGTGT	CGTCCCATAT	TCAGCTGAGC	CTTGTCTCTA	TTTCTGCCAC	AGGGTCTCTA	CGTCCGAGCA	17920
	CTGCTGGTAG	AGGGGCTGGG	GTCAAGGCGAG	GGGCGGCTGAG	TTTTCCGCGC	CGTCTGGGTA	CGCTTGAGTA	17990
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	AGGCTGTGAT	AAAGGCGCAG	AATCCCTCTC	CGCTGGAGCA	GAGCTGGGAG	AGACAGAGAG	TGGGCGCGCA	18130
	TTTCAAGGCA	CGAGGCTGCG	AGTGGGCGAG	CGTGTGGTGG	TCGACGTGGG	CGTGGGGGCG	GGTCTGTGAT	18200
	CAAACTCGCT	GGGCTGTGCG	CTTCTTGAGC	CGTGTGGGCG	GGGCGCTGAG	GGTGTGGGCT	GGTGGAGCTC	18270
	CGGAGCTCTA	GCAGGTGGCT	ATCTCTCTCT	GTGAGAGGCA	CGCTCTGAGC	TTATGCTAGT	GTCTGCTGCT	18340
	TGGTGTAGG	TGAGGCTCTG	GTGGAGGCTC	CGGAGCTCTA	TGCTTTATTA	TTGTTTAAAC	AACTATGTGT	18410
	CGTGGCTCTG	CGTGTGTGCT	AAATGGGAAA	AGAGCACTCC	ACCTCAGAGC	AATTACCTAG	CGCTGGAAAC	18480
	CGGGGTGCTG	CGTGTGCTCG	TGAGATCTCA	GGCTATTGCA	GAAGTGTGCT	AGAGGATCTG	TGAGAGCAAG	18550
	TACATGTGGG	GTCTGAGGAG	TGAGTGGAGT	GAGTATAGCG	GGGGCTCTAG	CGACTGGTGG	TTTAGAGCA	18620
	CTATGGGGCG	TGAGGCTCTG	GTGGAGTCTG	GTGACAGGCA	GGGCTCTGAG	AGAGGCTCTG	ACAGGATCTG	18690
	CGTGGCTCTG	GATCAGACGC	ACATATGAGC	ACATGTGCTG	TCATGTGATG	CCAGCTGCTG	ACAGCTGCTG	18760
	CACAGCTGCG	CGAAAGTCCC	AGGAGCTGGA	GAGGCGAAGC	ATGAGGCTCT	ACAGGCTCTG	CGGCTGGCTC	18830
	CACAGCTGTA	GTCTGAGCAG	TTTGGAGAGC	CGAGGCGAAG	GGATCTGCTG	AGCCGAGAGC	TTTAGAGCA	18900
	CTCTGAGGAA	GTATGATGAA	CGGCTATCT	ATGAAATATC	AAAGAAATAT	TGAGTGTGAC	GGTGTGGTGT	18970
	CGGCTGTGAG	TTGCACTACT	TGGGAGGCTG	AAAGTGGAGG	ATCACTTGAG	CCGAGGAGCT	GGAGCTGTGA	19040
	GTGAGCTGAG	ATTGACACAC	TGTACTGAGC	CGTGGTGGAC	AGAGTGGAGG	CGCATCTTCA	CAACAACTAA	19110
	GAACTAGTGA	AAATGAGCTT	CTTGGAGAG	AAACATTATG	TAGGAACTTA	CGATCTACAC	AGAGGCTGAC	19180
	TGCTGTCTCT	GGTCTGATG	AGATGAGATG	CGGAGTCTCT	ACACATCTAC	CCGAGAGCTA	GGTGTGATG	19250
	ACCAAGGGG	GGGCTGTGAT	AAAGAGGATG	CGGAGGAGCT	CTATATAGCA	TGACATCAAG	GGTGTGCTAG	19320
	GAGGGGAGG	ATTCACTGAT	AGTACTGCTT	GGTACACAGG	GAACTATGGA	TAACTTAGAG	ACCTTAGAGG	19390
	CGTCTCGGCA	ACAGGGGCTA	ATCAGAAAGC	AGCATGGGGG	GGTGGCTATC	AGAGATGAGG	CGCTTAGAGC	19460
	TGCACTGAGT	TGTTCTATCA	GATGTGTGAG	AGAAAGGCGG	TGTACTCTCT	CACACACAGA	CAGAGCTATA	19530
	CTGCGACAGA	CAGACACACA	CACAGACATG	CATCTATGGA	TGCTCTGTGT	TGACCTCTGT	CCGATGAGGA	19600
	AAOCCATCTA	TGTGCTATCA	TGCGACGACA	CAGGCACTGG	TGGGCGCATC	CGGACACCTA	CAACTTAGAGT	19670
	CTGATGATGA	GGGCTTTCTT	CTGAGCTGTG	CGGCTATCTT	CTAGGATCTG	AGCATGTGCT	GGTCTGAGCT	19740
	CGATTCTATC	ACAGAGTTTG	GAGAGACGCG	ACATTTTCTC	TGGGCTGTAT	CGGCTCTGAT	GGTCTCTGCT	19810
	CGATCTCTAT	AGAGAGGAGC	GATATGAGCT	CGGCTCTGCT	GTGGGCTGCT	TGAGAGGAGC	CAGGCTCTCT	19880
	TGAGTGTGCT	TAGTGTGCTA	GGAGCTATG	TGAATCTTGG	CTTAGAGAGT	TCTTACCTCT	TTTGCTGATCA	19950
	GGAGTGTGCT	TAAACCAAGC	ACTGTAGGCT	TGCTGTGGCG	GGGCTCTGCT	GGGCTGAGCT	AGGCACTGTA	20020
	TGAGAGGAGC	AGAGAGTGTG	TGGGAGCTG	CATCTTCTCC	ACCTTGTGCT	TGCTGGGGGA	GGCTGTGGGG	20090
	CGCTGTGCTT	TCCTGTCTTG	CCGATGTGCG	GATTTGGAGG	CGGCTGGGCT	CGGCTGGGCT	TGCTGTGCTG	20160
	GGTGTGGGTT	TCTCTGCTCT	ATGGGACTTA	GGGCTGTGCT	CTAAACCGAG	CGGAGAGGCT	TAGGAGAGAG	20230
	CGAGGCGGCG	GTCAACCCAG	CGCTCTCAGG	AGGCAAGGAG	GGATTAACAC	ACGAGAGAGC	CGGCGGGGCT	20300
	CGCTGCTCTG	CTAGTACAGG	TGCTCTGGCG	CTGGAGCTCT	TGTGCGACTT	CAGGAGGGAT	TCTGATCTGT	20370
	CTGAAATCTA	AGGCTAGGCG	AGGCTGGGCT	CGCTGACTTA	ACAGCTGTCT	CTTCTGTGCT	TTTCTGCTCT	20440
	GTGAAATCTT	CTAGTAGAGA	AGGCTATCTG	ACATCTCTCT	AGCATCTCTG	TGCTGAGTCT	TGGGCTGCTG	20510
	AGGAGAGAT	CGGCGAGC	CGGAGAGCTG	GGGCTGTGGG	CAGGTTTGGC	GTGTCTCTCT	GGAGGGGAGC	20580
	TGGGCTGGCG	GTGAGCTCTG	TGAGCTCTCT	TTTTCCGCCA	GGGATGTGCG	TGGGGGCGAG	GGGCGGGCGC	20650
	GGGCTCTCTG	CTCTCGAGGG	GGTGGAGCTG	CTGTGCGGCT	AGCATCTCTG	GTGAGAGCTC	ACTGACAGAG	20720
	GTGCTCACTA	GGGCTGCTCT	CTGGGGTCTG	TGAGGAGGAG	CAGGTGTGCG	GTGAGGAGG	GGGCTGAGG	20790
	ACTTGGCGAG	GGGCTGCTCT	TGAGGAGCTA	GGGCTGTGCT	AGGAGCTCTG	GATHTCTCTG	AGGAGAGGAG	20860
	CGGCGGGGCG	GTAGCTCTGG	GGGCTGTGAG	CGAGCTGTG	AGGCTATCTG	GATTAAGAGC	TAGTGTGGCG	20930
	AGGCTGTGAG	CGGCTGTGAG	GTGCGGAGCT	CTGTGTGCTA	TCTCAGGGCG	GATGGCTCTG	AGGCTGTGCT	21000
	CAGCTGTGAG	AGGCTGTGAG	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	TGCTGTGCTG	TGCTGTGCTG	21070
	TGCTGTGCTG	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21140
	CGGCTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21210
	TGCTGTGCTG	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21280
	ATTTTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21350
	CGGCTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21420
	CGGCTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21490
	CGGCTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21560
	CGGCTGTGCT	AGGCTGTGCT	GTGCTGTGCT	AGGCTGTGCT	CGGCTGTGCT	AGGCTGTGCT	AGGCTGTGCT	21630

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	CAGTTCODEA	CAGGCTGGGG	CTGGGCTGCA	CCCGAGGCG	AGCTTTTCTC	CAGCAGGAG	CGGGCTTCCA	21700
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	CCACGCCCAC	CATCCAGGTC	GAGACCGTGA	GAGGAGCCCT	GGAGCTCTCG	GGAATTTGGC	GTGACCAAGG	21840
5	GTGTGGGAGT	TACACAGGTC	GAGACCGTGC	ACCTGGATGT	GGGTCCCTGT	GCCTCAAAAT	GGGGGGAGGT	21910
	GTGTGGGAGG	TAAATATCTG	AATATATGAT	TTTTTCAGTT	TTGAAAAGAA	TCTCAGTFTT	GAATCTGTAAT	21950
	GTGTACCTGTA	TAGACACAC	TGTATGCAT	TACAGAAAGC	TGTGAGTGA	CGGGGTGTGT	GTCAATGCGG	22010
	GCCTATGGC	TGCTTTGTGA	TTTAGGGAAG	TCTATAGATG	AATGGGTTTG	TGTCTAGTGG	GGGCCCATCTG	22120
	CTCTGGTGGG	CTGGGGAGGT	TTGTGATGCT	GTGAGGAGCT	AGGGGAAGGA	GGGTATGGGA	TAGAACATGG	22190
	GAGCCCCCAC	CTTGGAGAAC	ATACACATAA	GTCCAGGCCC	GAGGAGCAGC	AGGATGATCT	GGGGCCGACAG	22240
10	TTTGGGGGGG	GGGATCATGG	AGGGGCTGGC	CAGGCTGGCA	GGGATGATCT	GGGACCCACG	TGGGCTGGCA	22300
	GGGCTGATGG	GGGGGCTGG	TCCTGGTGGC	GGGAGAGATG	GGGACCTCTC	GGGATGATCT	CTCTCCCTCT	22400
	GGCTCCACCA	TGACGACCGT	GATCCGGGAT	TGCTTTCCCT	GTGACATCTC	TTCTGGGCTAT	CAGCTTTTCAT	22470
	GGAGTGGGGG	GGGAGGGGCA	TGACACCATC	CTGTATATAA	TCCAGGATTC	TCTGCTGCTG	ACGCCGCCAC	22540
	TCAGGTTGAA	AGTCACATCT	GGCTCTTGGC	CATCTCTCTA	AGGATAGACC	AGGATTTCTG	TCTCTGAGAG	22610
15	TTGGGTTAGG	TGGGCGAGTG	GAGGATCTGG	ATCACAGAGC	CTTCAAGGTT	GGGCTGGTGA	TGCTCTCTCA	22680
	TGCTCTATCT	ATCTTCCAGT	CTCATCTGTC	ATGCTTCTAT	CATCTCCGAG	TCTCATCTGT	CTTCTGCTTA	22750
	TGCTCCAGTC	TCATCTGTCA	TGCTCTTACC	ATCTCCGAGT	CTCATCTCTT	ATCTGCTTAT	TCCTCATGCT	22820
	CATCCAGACT	PACCTCCGAG	GGGGGGTGGC	AGGCTGGCAG	TGGAGCTGGA	CATAGCTGCT	TGCTCAGGCA	22890
	SHAGGAGCTG	GAGGATTTGG	AGGAGACAGG	AGGGCCGCTC	CAGAGGGGAC	CATGTTGGCT	GTGAGGAGAC	22940
20	AGGCTCTCTC	CAGAGTTGGG	CTTGGGCCAC	ACGAAACCGA	GGGCCCTGCG	TGATGGGCTC	CAGAGCTCTC	23030
	CAGGAGCTCC	TGATGGGGGC	CTTATGGTAT	GGGCCGGGTC	TACTAGTGCG	ACCTTGGACA	GGGCTTCTGG	23100
	TTTGAAGTCA	CGCCCGGAGT	GGCTGGTGTG	GGGGTGGGGG	CTTATGGGCA	CTGGATATGG	CGTCAATTAT	23170
	TGCTGTGCTC	TCAGAGAAAT	TCTGAGTGAC	CGAGCTTAAT	GTATATGGTG	GGCCGAGCTC	CACAGACTGT	23240
25	GTGTGAATGT	CAGCTTGGTG	CTTGGAGGCC	CGGTATAGGA	AGGTTGAGGA	AGGTTGAGGA	CTTGGAGGCC	23310
	GGCTGTGGGG	GGGCTTTGCC	CTGCAAACTG	GAGGAGAGGG	GGCCCGGGCG	CGGTGGGGCG	AGGACTCTCA	23380
	GTGAGAGGTT	GGACAGAGCA	GGGCGGGGAC	TGCTCCAGAG	CAGAGGCGCG	TGCTCAGGCA	CACCTGGGTT	23450
	TGAATCACAG	ACACAGAGCT	GAGGCTATTC	TTGAGCTATC	CATCTCTTAC	AAAGCTCCAC	AGCTCTGTTT	23520
	CTCGGGGTGT	TTTTTGTGTA	AAATTTACTT	AGGATTACTT	ATATTTCTGT	CTAAGATTTT	AGAGCTTTAA	23590
	AAAAAGATT	TGCTTGATA	TGGCTTAATC	CAGTAGAGAC	CTACTTTTAT	TGCTGTTTAT	TATTTAATAT	23660
30	TATTTATATT	ATTAGAGATC	GTGCTTACTC	TGTCAACGAG	GTGTGTAGTG	CAGTGCGACA	GTGATGGCTC	23730
	CTGTATGGCG	AAAAOCCCA	GGCTCAAGTG	ATGCTTCGGG	CTCAGCTTCC	CAGAGTGCTG	GGTTACAGGG	23800
	TGTGAGCCAC	TGCGCTTTGG	TGGCACTTTT	AAAGAGACT	ATGATAGTCT	AGGTCAGTGT	GTCTCCAGC	23870
	CTGTATCTC	AGTATGTTGG	GAGGCTCCCG	CAGAGAGATT	GTCTGAGGCT	AGGATTTTGA	GAGGAGCATG	23940
35	GGTACATAG	GGAGACCCCA	TCTCTACAAA	AAATGCAAAA	AGTTATCCGG	GGCTGGGGTC	CAGCATCTGT	24010
	AGTCCGAGCT	CTGGGGGAGG	CTGAGTGGGA	GGATGCTGTT	AGCCCGGGAG	GTGATGGGTC	CAGTGAAGTG	24080
	TGATTGTATC	ATGAGCATCC	AGGCTGGGCA	ACAGAGAGAG	ACCTGTCTCT	AAAAAAGAAA	AAAAAAGAAA	24150
	AGGAGAGGG	AGGAGAGGAG	AGGAGAGGAG	AGGAGAGGAG	AGGAGAGGAG	AAAGAGGAGG	AAAGAGGAGG	24220
	AGGAGGCTCT	CGTAGGCTCT	AGGTAGACTG	TCAUATCTCA	GAGCAAAATG	AAAAATACAA	AGTTTAAAGG	24290
	GGAGAGAA	ACCCAGGCTC	TTTGAGCTTC	CTTAGGGCTG	AACTTCATCT	CAGGAGCATC	CGTTTCCAGC	24360
40	ACAGAGCTGT	ATGAGGCGAG	TGAGTTGCAA	GGGAGAGGCA	GGGAGAGGCA	GGGAGAGGCT	GAGGCTGTGC	24430
	GTGACAGCTG	CCAGGCGGCC	TGAAAGGGAG	TGCTTTTCTT	CCGCTGCGAG	CGGACCATCT	CTGCGGGTCC	24500
	TGACAGTGT	GTAGGCTGCT	ATGCTGTGGG	CAGGTGCCCA	CTTGGGAGAG	ATGCTGTGCA	GGGGGCTTGC	24570
	CAAACTTTGG	TGGGTTTTCAG	AAAGCCCGAGG	CAGTTTGGGC	AGGCCAAATT	ACAGGCCCTC	CGCAAGAGAT	24640
45	CCGAGCTGCT	TCTCTGGGAA	CTGTGATATG	TGTACCCCGG	AGGCGAGAGG	CTGTGTGAGG	CTGCAAGGTC	24710
	AATCAGCTGT	CGCAGCCAGC	CGATCTTAAG	GTATCTCTGC	ATTATCTGCT	GGGCTGTATA	TGGCGTGAAT	24780
	GCTGCTTGA	AGTGGAGGAG	GGAGGCTAGG	GAGATCTCAG	GGGGGAGAGT	GAGAGAGGCC	ACTGGCCACT	24850
	GCTGCTGTTT	AGATGGAGGA	GGGGGCTCCC	AGCCCAAGGA	TGGGGGAGAG	CGCTCTCATG	TGGAAAAAGCA	24920
	AGCAATGCTC	CGGCTGCTGT	AGGGGACAGG	GGCTTCCCCA	CGCTCTGATT	TGAGGCCAGT	GGGACCTGTT	24990
	TGAGCTTTTCC	GGGCTGTCAG	GCTGTAGAGT	GATGCTTTTG	TGCTGAGCCA	CTAAGGTCGA	GTGATCTGTC	25060
50	ACACGCAAAA	ATGGATATAG	AGTACGAGGA	AATGAATACA	GGGACGTTTC	TGAGGCTGAC	TCTCAGCCA	25130
	CGCTGGGG							25138

Example 5

- 55 Comparison of the above-described genomic hTC sequence and the sequence of the hTC cDNA (Fig. 6; corresponding to SEQ ID NO 2) made it possible to elucidate the exon-intron structure of the hTC gene. The genomic organization of the hTC gene is illustrated diagrammatically in Fig. 7. The coding region of the hTC gene is composed of 16 exons which vary in size between 62 bp and 1354 bp (see Table 1).
- 60 Exon 1 contains the translation start codon ATG. The translation stop codon TGA and the 3'-untranslated region lie on exon 16 (Fig. 8). No possible polyadenylation signal (AATAAA) was found either in exon 16 or in the 3195 bp of the following

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3'-flanking region. The exon-intron transitions were determined on the basis of the consensus sequence

		5'-Exon			Intron				3'-Exon							
5	Pre-mRNA	A/C	A	G		G	T	A/G	A	...	N	C	A	G		G
	Frequency (%)	70	60	80		100	100	95	70		80	100	100	60		

and listed in Table 1. With the exception of the 5' splice site between exon 15 and intron 15, all the exon-intron transitions are in accord with the published (Shapiro and Senapathy, 1987) splice consensus sequence. The sizes of the introns are between 104 bp and 8616 bp. Since only part of intron 6 was isolated, it is not possible to determine the precise length of the hTC gene. Based on the part sequence of ~4660 bp, which was obtained from intron 6, the minimum size of the hTERT gene is 37 kb.

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Introns 1-5 and the 5' region of intron 6, are contained in contig 1:

Intron 1: bp 11493-11596 (SEQ ID NO 4);

Intron 2: bp 12951-21566 (SEQ ID NO 5);

Intron 3: bp 21763-23851 (SEQ ID NO 6);

5 Intron 4: bp 24033-24719 (SEQ ID NO 7);

Intron 5: bp 24900-25393 (SEQ ID NO 8);

5' region of intron 6: bp 25550-26414 (SEQ ID NO 9).

10 The 3' region of intron 6, and introns 7-15, are located in contig 2 at the following positions:

3' region of intron 6: bp 1-3782 (SEQ ID NO 10);

Intron 7: bp 3879-4858 (SEQ ID NO 11);

Intron 8: bp 4945-7429 (SEQ ID NO 12);

Intron 9: bp 7544-9527 (SEQ ID NO 13);

15 Intron 10: bp 9600-11470 (SEQ ID NO 14);

Intron 11: bp 11660-15460 (SEQ ID NO 15);

Intron 12: bp 15588-16467 (SEQ ID NO 16);

Intron 13: bp 16530-19715 (SEQ ID NO 17);

Intron 14: bp 19841-20621 (SEQ ID NO 18);

20 Intron 15: bp 20760-21295 (SEQ ID NO 19).

The 3'-untranscribed region is also located in contig 2 at position 21960-25138 (SEQ ID NO 20).

25 The individual sequences of the abovementioned introns are as follows:

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Intron 1 (SEQ ID NO 4)

GTGGGCTCCCGGGGTGGGTCTGGCTGGGTTGAGGGCGGCCCGGGGAAACCAGCAGCATGCGGAGAGCAGCGCAGG
CGACTCAGGGGGCTTCCCGCGCG

5 **Intron 2 (SEQ ID NO 5)**

GTGAGGAGGTGGTGGCGGTCCAGGGGCCAGGGCCAGAGCTGAATGCAGTAGGGGTCAGAAAAGGGGGCGGGCGAGGCC
CTGGTCTCCTCTGTCTCCATGCTACGTGGGCGACAGTGGCTTTTCCTCAGGAGCTCGAGTGGACAGGGTGTCTCTGGG
TCTCCTCTCCTCTCTGTCCAGTTTTCAGTAACCTTACGAGGTTCACTTCACTCAGTTTGTATGACACAGCGGTTTCCAGGCGC
GGAGGCGACAGCGAGTGAACAGGAGGAGGCTGGGCGCGCCAGTGGAGCGGGTTGCCGCAATGGGGAAGATGCTGCTGGGGA
CAGAGACGCTCTGGCGAGGTGGCTGCAGGTTACCTATAATCTCTTCGCAATTTCAAGGTTGGATAGAGGTTGGGA
10 GAGAACCGCTCTCTTCGGGTTGGAGGTAAAGGTTTTCGAGGTGCACGTGTGACGCAATATGAGGTTTGTGTTTA
AGATTAAATTTGTGTGTTGACGGCCAGGTGGGTTGGCTACCGCGGTATCCAGCACTTTGGGAAGCTGAGGCGAGTGGG
TCACTCGAGGTCGAGGATTTGAGACGAGCCTGACCAACATGTTGAACGCTTCTGTACTAAAAATACAAAAATTAAGTGT
GGCATGGTGTGTTGCTCTGTAATCCAGCTACTTGGGAGGCTGAGGCGAGGAAATCACTTTGAAGCCAGGAGGCGAGGCGC
15 TGCAGTGAAGTGAATTTGTGCTTGTACTCCAGGCTGGGCGACAGAGTGAAGCTCTGTCTTTAAJAJAJAJAJAGTGT
GTTTAATTTGTGCTGAGGAGAGGTTAGGGAGGGAGATAGAGCTGTTCTCAGCAGCAGATCTGGTCCGCTCATCTTTAGGTAT
GAAGAGGCGACCATGGGAGCAGAGGACAGCAGATGGCTCCAGCTGCTGAGGAGGAGCAGTGTTTGTGGGTTGTGAGGG
ATGGTGTGTTGGGCGCTGGCGGTGTCCCGACCGCTGTTTCTCGATTTGATGTGTTGAAGAACTCCGCTGCAGCGCCCTTT
TGGCTCCGAGTCTCCGAGGCGCTACCGTGGCAGCTAGAGAGAGTCCGATTTACCGCCCTCCCGAGAACTCCGAGAGC
20 ATGTAAAGACTTCCGCGCATGACAGCAGGAGGAGTGAACCTCTTGGGCGCTCTTTTCTTTCTTTTCTTTTATGTTGG
AAAGTGCATATACAGAGGATTGGCACTCTGAAGAGGTTTCTGTGACAGTGCAGAAATGCTAAAGTCCGGCGTTTCTTA
GAGCAGGTGTGCTGAAGTCTGGCTCTGTGCTGACTTGAAGTCTACCGCATCGAGCGAGCTGCTCAGCTGCTGCTC
GAGCTCAGGTGGACACCGCGAGTCAGATAAGGCTCATGCAACCGAGTTTGTCTTTTGTGCTCCAGCTCTCTCTGAGT
GAGAGTTTGAATCTCTGTATCAGGACTCTGGCTGTGATTGTCTTCTGACTTCAGATGAGGTGAGATGCGCCCTGG
25 CTATAGCAGGAGTGAAGGCTGTGCTCCCGGTTGCTCCTGTACAGTGTGAGGTTGAGTGAAGGCTTCCCGCCAGGTGTCCGT
GTCAAGTGTAGGTTGAGTGAAGGCGCGGCCCGGGTGTCCCTGTCCGTGACAGCTGATTAAGGTTGGGCGCGGGGTGT
CCCTGTACAGTGTAGGTTGAGTGAAGGCGCCATCCCGGGTGTCCCTGTACAGTGTAGGTTGAGTGAAGGTTGGCGCG
GTGTCCCTGTGCTGGTGAAGTGAAGTGAAGCACTGTCCCGGGTGTCCCTGTACAGTGTAGGTTGAGTGAAGGCGGGTCC
CCGGTGTCCCTGTACAGTGTAGGTTGAGTGAAGGCGCGGCCCGGGTGTCCCTGTACAGTGTAGGTTGAGTGAAGGCG
30 GTCCCTGGTGTCCCTCCAGGTATAGGTTGAGTGAAGCACTGTCCCGGGTGTCCCTGTACAGTGTAGGTTGAGTGAAG
CGCGGCCCCCGGGTGTCCCTGTACAGTGTGAGGCGGTTGAGGCGCGCTGTCCCTGGGGTGTCCCTGTCTGTGTAGGTTGAGT
GAGGCTCTGTCGCGAGGTGTGCTTGGGCTTGTGCTCACTTGAAGCTTGTGCTGAATGTTGCTCTTATAGGCAAGCT
GGGCGGTTGGCATTGCTGGTGTAGATGTTGCGAGCGAGGTGTGGTGGCAGAGCTATGTTTTTCTGATGCTCGGCTCT
TCTGTTGCACTGCTCGGTTGCAATTTGCTACCGGGACAGGAGTGCAGGCTCTCGCTCCCGGTTGGCGAGCACTGCGAG
35 GCACAGCTTGAAGTGGGTTGGCTGTGTTGGGCTGGCTTGTCTCAGCAGTGTCCCGCGAGATGATGCTGGCGAATATCC
TCTGGCAGTGTGCTGATGCGGAGCTGGAGCTGGGCTGGCTGTGTGTGTGTGCGCAAGTGTGCTGGAGAGATCCGAGAA
AGGGTGTCTGTGCGGTTGAAGGAAAGCAAGTCAACCGAGCGGCTCACTTGTGCTGTTTTTCCGAGGCTGGGCTGTGG
TGGCGCCCTTGGTGGGTTGGACAGCTGTGCACTTATTTGGGCGAGTGGCGGCTCATGCTTGAAGTGGGCTGTGCT
CGAGTCCCGGCTGCAGATGGATTGAGCTCGAGCAGAGGTTGGAGTGTCTGTGCTGTGTGCTGTGTGAGACGAGGTCG
40 GAGGCGGGTGTGCTGGGCGAGGCTTGTGACAGCTTCCCTTGTGGGCTTGAATTTGAATTTGAGTGTATTTACCTTGAAG
TGTGCTGTCCAGTGTGATGCTTTTGTGGTGTATTTCTTCACTGCTTGTGAGTCTTGAATTTGAGCAGTGTATTTGAACCT
GCTTGAAGTGTGCTGTTGCTGACGCTGTGTTTGTGATGAGTATCTCAACATCAGGCACTTTCAGTGTGTGTAJAJ
ATACTTGAAGTGTATGACTGCTTTGAAGTATCTGATTCGTGATTTTTTCTTGTGAGGCTGTGTTTTGAGTGTGA
45 AATCATTTGTATCAGTGACTTTGAAGTATCTTGAAGTATTTCTGTGATTTCTTGAAGGAGTGAATTTGAACACT
GTTTATGTTCAAGATATGTAGAGTATCAAGATACGAGAGTATTTGAAGTATCATTTTATTTAGTGTATTTGAAGTGT
GTTTGAAGTGTGTATTAACCAATTTTGAAGTGTGGGAGGCTGCTTGTGATGATGATGTTGGATGGTTCGAG
AAGTGTCCATGTTGAATTTGAGTGTGTTGAATGTGGGAGTCAATGTTGATATATGAGCTATTTAAGTGTGAGTGTGA

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- CAGAGAGATTACAGTGTGCTGATTCCCGGCTGTTCTCGGTAATGGTGTCTGTGTTTATGGATGGGCTCTTCCA
 TTCTCTTTAGGCTTTGGTTTATTGTTGTTTTCGGGCTCTTGAAGGAAAGTTTCGATTATGGATGTTTGAACTTCTCTT
 TCTAAACAGAGCATCTGAAGTTGCCGTTTCTCTTAAAGCAGGGATCCCGAGGCCCTGGCTGTGGAGTGGCAGGGCTC
 GGGCCCTGTTAGGAACCCGGCCACAGCGGGAGCTAGGTGGGTGTGGGGAGCCAGGCTTCCCGCTGAGCCCGCCCC
 5 TCTCAGTACAGCATCGCATCGCGTGTCTCAGAGGGGCACACACCTACTCAGAACCTGTGCTGAGAGGGTCTATGATTT
 GTGCTCTCTATGGGAATCTAATGCTGTATGATCTGAGGTGGAAACGTTTGCTCCAAAGCCATCCCTTCCCGCATGCTG
 TCTGTGGAAAAATCGTCTTCCACGAACCCAGTCCCTGTACCAATAGTTGGGAGCCCTGTGCTAAGAGCTGCTTCA
 GCGAGCTCTGCTCAGTGTGATATAATTGGCTTTTCTGTGTGAGTCCAGAAATATACGGATTCTGTGTATGCTTTCGGC
 CGACCTCAGACCGCATGGCGTATTGTGGGGGTGTTGCCCTGCTCTGGGTTGGGAGGGTGCAGGCCCATCTGACCTTCT
 10 GTTACTGCTTCCAGGTGGTTCTCAGGGTGAATCGTACTCGATGGGTTTACGCCACGCCCTGCGCCAGCTCTGT
 GGGGCTGGGGAACATGCTGAAGCAGAGTCAACGTGGCGCTTTTGATGGCTCACAGCTCGAGGCTCTGTTGTCCG
 TGTATGTGTGTGTCAAGTGTCTGCTCAGATCTGTCTTGGGAGCGAGGGGCTTAGCAGGTCCCGTAGTAATGACAGGC
 GTCTCTGGGGAGTCTCGGAATAGGAGGTGGGGGTGGCGGCTCTCTCTCCCGCTCTTCAGACTCTTCTCTGCTGTGTGT
 GTGCTGCACTGCACTGCTGCAATCCCTCCAGCACTGGGCTGGAGAGGCCCGGAGCTCGATGGCACTTGTGCCACGT
 15 GACTGTGATGGCAGTGGTCAAGCGGGTCTGATGTGTGTGACTGTGGATGGCGTTGTGTCACAGGGTCTGATGTGTG
 GTGACTGTGATGGCGGTCTGTGGGGTCTGATGTGTGACTGTGGATGGCGTGTGGGTCTGATGTGTGTGACTGTGG
 ATGGCGGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGGTACTGTGGATGGCGGTCTGT
 GGGTCTGATGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGT
 TGGTACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACT
 20 TGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGG
 CGGTCTGTGGGTCTGATGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGT
 CAGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTG
 GGGTCTGATGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGT
 25 TGTGATGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGT
 GACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGG
 GCGGTGTGTGCGGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCAG
 TCTGTGATGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGT
 30 GTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACT
 GACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGG
 GCGGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCAGTGG
 GTCACAGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGG
 35 GTGTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGAT
 GTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACTGTGGATGGCGTCTGTGGGTCTGATGTGTGTGACT
 ACTTGTGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGG
 GGCTTGGCGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGG
 ATGGCTCTCTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGGGTCTGTGG
- 40 **Intron 7 (SEQ ID NO 11)**
 CTCCTGGGACCTCCCTGCGAGGTTGGGCAATGGACTCCAGCAGTGGGTCTCTCCCTGGGCAATCACTGGGCTCATCAACC
 CAGACAGTCTTGGGCTGCGGAGGAGTGGGAGGAAATGAGCTGTGAGGGGAGATGATGAGTGTGTGCTTGGGAAATC
 TGAAGCTGGGAGCTGCGAGGCTGGGACAGCTGTGTCATTCAGGACCTGTCTCAGCTTTGACTGTGGGAGGCTCTCTCAAT
 CCGCAGTGGCTTGTGTGATGATTGGATATGTCTCTCTGAGGAGTTTGAATCTTGAAGGCCAAGGAAAGCTGCTCT
 45 CCTTTAGGAGGAGCAGGCTATTTTGGAGCTGTGCTGTCCAGCTGTGGGCTCAGTGTGTGTGTGAGCTGAGGAAAGG
 TGTGCCCTCTTGAAGAGAGGGGGGTCTTTAGGACAGCCCGGTGAGGAGGCTGTGTGATGCTGAGTGTGTGAGTGT

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Characterization of the exons showed, interestingly, that the functionally important hTC protein domains which are described in our Patent Application PCT/EP/98/03469 are arranged on separate exons. The telomerase-characteristic T motif is located on exon 3. The RT (reverse transcriptase) motifs 1-7, which are important for the catalytic function of the telomerase, are located on the following exons: RT motifs 1 and 2 on exon 4, RT motif 4 on exon 9, RT motif 5 on exon 10, and RT motifs 6 and 7 on exon 11. RT motif 3 is shared by exons 5 and 6 (see Fig. 8).

Elucidation of the exon-intron structure of the hTC gene also shows that the four deletions or insertion variants of the hTC cDNA which were described in our Patent Application PCT/EP/98/03469, as well as three additional hTC insertion variants which are described in the literature (Kilian et al., 1997), in all probability represent alternative splicing products. As shown in Fig. 8, the splicing variants can be divided into two groups: deletion variants and insertion variants.

The hTC variants in the deletion group lack specific sequence segments. The 36 bp in-frame deletion in variant DEL1 in all probability results from using an alternative 3' splice acceptor sequence in exon 6, resulting in a part of RT motif 3 being lost. In variant DEL2, the normal 5' splice donor and 3' splice acceptor sequences of introns 6, 7 and 8 are not used. Instead exon 6 is fused directly to exon 9, resulting in a displacement arising in the open reading frame and a stop codon appearing in exon 10. Variant Del3 is a combination of variants 1 and 2.

The insertion variant group is characterized by the insertion of intron sequences which lead to premature cessation of translation. Instead of the 5' splice donor sequence of intron 5, which is normally used, use is made, in variant INS1, of an alternative, 3'-located splice site, resulting in the insertion of the first 38 bp from intron 4 between exon 4 and exon 5. The insertion, in variant INS2, of a region of the intron 11 sequence likewise results from using an alternative 5' splice donor sequence in intron 11. Since this variant was only described inadequately in the

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literature (Kilian et al., 1997), it is not possible to determine the precise alternative 5' splice donor sequence in this variant. The insertion of intron 14 sequences between exon 14 and exon 15 in variant INS3 comes from using an alternative 3' splice acceptor sequence, resulting in the 3' part of intron 14 not being spliced.

5

The hTC variant INS4 (variante 4), which is described in our Patent Application PCT/EP/98/03469, is characterized by exon 15, and the 5' part region of exon 16, being replaced by the first 600 bp of intron 14. This variant can be attributed to the use of an alternative internal 5' splice donor sequence in intron 14 and an alternative

10

3' splice acceptor sequence in exon 16, resulting in an altered C terminus.

The *in vivo* generation of hTC protein variants which are probably non-functional and which could interfere with the function of the complete hTC protein constitutes a possible mechanism, in addition to transcription regulation, for controlling hTC protein function. The function of the hTC splicing variants is not yet known. Although most of these variants presumably encode proteins without reverse transcriptase activity, they could nevertheless play a crucial role as transdominant-negative telomerase regulators by, for example, competing for interaction with important binding partners.

15

20

The search for possible transcription factor binding sites was carried out using the „find pattern“ algorithm from the Genetics Computer Group (Madison, USA) GCG Sequence Analysis program package. This resulted in the identification of a variety of potential binding sites for transcription factors in the nucleotide sequence of intron 2, which binding sites are listed in Tab. 2. In addition, an Sp1 binding site was found in intron 1 (pos. 43), and a c-Myc binding site was found in the 5'-untranslated region (cDNA position 29-34, cf. Fig. 6).

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Example 6

In order to ascertain the start point(s) of hTC transcription in HL 60 cells, the 5' end of the hTC mRNA was determined by means of primer extension analysis.

5

2 µg of polyA⁺ RNA from HL-60 cells were denaturated at 65°C for 10 min. 1 µl of RNasin (30-40 U/ml) and 0.3-1 pmol of radioactively labelled primer (5'GTTAAGTTGTAGCTTACACTGGTTCTC 3'; 2.5-8x10⁵ cpm) were added for primer annealing, and the whole was incubated, at 37°C for 30 min, in a total volume of 20 µl. After the addition of 10 µl of 5xreverse transcriptase buffer (from Gibco-BRL), 2 µl of 10 mM dNTPs, 2 µl RNasin (see above), 5 µl of 0.1 M DTT (from Gibco-BRL) 2 µl of ThermoScript RT (15 U/µl; from Gibco-BRL) and 9 µl of DEPC-treated water, primer extension took place, at 58°C for 1 h, in a total volume [lacuna]. The reaction was stopped by adding 4 µl of 0.5 M EDTA, pH 8.0, and the RNA was degraded, at 37°C for 30 min, after having added 1 µl of RNaseA (10 mg/ml). 2.5 µg of sheared calf thymus DNA and 100 µl of TE were then added, and the mixture was extracted once with 150 µl of phenol/chloroform (1:1). The DNA was precipitated, at -70°C for 45 min, after adding 15 µl of 3 M Na acetate and 450 µl of ethanol, and then centrifuged at 14,000 rpm for 15 min. The precipitate was washed once with 70% ethanol, dried in air and dissolved in 8 µl of sequencing stop solution. After 5 min of denaturation at 80°C, the samples were loaded onto a 6% polyacrylamide gel and fractionated electrophoretically (Ausubel et al., 1987) (Fig. 5).

25 In this connection, a main transcription start site was identified which is located 1767 bp 5' of the ATG start codon of the hTC cDNA sequence (nucleotide position 3346 in Fig. 4). In addition to this, the nucleotide sequence around this main transcription start (TTA₋₁TTGT) represents an initiator element (Inr), which, in 6 out of 7 nucleotides, matches the consensus motif (PyPyA₋₁Na/iPyPy) (Smale, 1997) of an initiator element.

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It was not possible to identify any unambiguous TATA box in the immediate vicinity of the experimentally identified main transcription start, which means that the hTC promoter has probably to be classified in the family of TATA-less promoters (Smale, 1997). However, a potential TATA box from nucleotide position 1306 to nucleotide position 1311 (Fig. 4) was found by means of bioinformatics analysis. The subsidiary transcription starts which were additionally observed around the main transcription start have also been described in the case of other TATA-less promoters (Geng and Johnson, 1993), for example in the strongly regulated promoters of some cell cycle genes (Wick *et al.*, 1995).

Example 7

In addition to the start point of the hTC transcript which was described in Example 6 and identified in HL60 cells, a further transcription start region was also identified in HL60 cells. With the aid of RT-PCR analyses, the region of the hTC gene transcription start in HL60 cells was localized to bp -60 to bp -105.

The cDNA for this was synthesized using a First Strand cDNA Synthesis kit (Clontech), in accordance with the manufacturer's instructions, and employing 0.4 µg of HL60 cell polyA RNA (Clontech) and the gene-specific primer GSP13 (5'-CCTCAAAGAGGTGGCTTCTTCGGC-3', cDNA position 920-897). In a final volume of 50 µl, 10 pmol dNTP mix were added to 1 µl of cDNA, and a PCR reaction was carried out in 1xPCR reaction buffer F (PCR-Optimizer kit from InVitrogen) and using one unit of platinum Taq DNA polymerase (from Gibco/BRL). 10 pmol of each of the 5' and 3' primers defined below were added as primers. The PCR was carried out in 3 steps. A two-minute denaturation at 94°C was followed by 36 PCR cycles in which the DNA was first of all denatured at 94°C for 45 sec and, after that, the primers were annealed, and the DNA chain was extended at 68°C for 5 min. The cycles were concluded by a chain extension at 68°C for 10 min. In all, six different 5' PCR primers (primer HRT5B: 5'-CGCAGCCACTACCGCAGGTGC-3', cDNA position 105 to 126; primer CSS:

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5'-CTGCGTCTGCTGCGCACGTGGGAAGC-3', 5'-flanking region -49 to -23; primer PRO-TEST1: 5'-CTCGCGCGCGAGTTTCAGGCAG-3', 5'-flanking region -74 to -52; primer PRO-TEST2: 5'-CCAGCCCTCCCTTCCTTCC-3', 5'-flanking region -112 to -91; primer PRO-TEST4: 5'-CCAGTCCGCCTCCTCCGCGC-3', 5'-flanking region -191 to -171; primer RP-3A: 5'-CTAGGCCGATTGACCTCTCTCC-3', 5'-flanking region -427 to -405) were combined with the 3' PCR primer C5Rback (5'-GTCCCAGGGCACGCACACCAG-3', cDNA position 245 to 225). Genomic DNA was also employed for the PCR, as a control, in addition to the Oligo dT- and GSP13-primed cDNAs. As Fig. 9 shows, a PCR product was only obtained with the primer combinations HTRT5B-C5Rback, C5S-C5Rback and PRO-TEST1-C5Rback, indicating that the start point for hTC transcription lies in the region between bp-60 and bp-105.

Example 8

Several extremely GC-rich regions, so-called CpG Islands, are located in the isolated 5'-flanking region, of about 11.2 kb in size, of the hTC gene. One CpG Island, having a GC content of > 70%, extends from bp - 1214 into intron 2. Two further GC-rich regions having a GC content of > 60% extend from bp -3872 to bp -3113 and from bp -5363 to bp -3941, respectively. The positions of the CpG Islands are shown graphically in Fig. 11.

The search for possible transcription factor binding sites was carried out using the "Find Pattern" algorithm from the Genetics Computer Group (Madison, USA) GCG Sequence Analysis program package. This resulted in the identification of a variety of potential binding sites in the region up to -900 bp upstream of the translation start codon ATG: five Sp1 binding sites, one c-Myc binding site, and one CCAC box (Fig. 10). In addition, a CCAAT box and a second c-Myc binding site were found at positions -1788 and -3995, respectively, of the 5'-flanking region.

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Example 9

In order to analyse the activity of the hTC promoter, PCR amplification was used to generate four hTC promoter sequence segments of differing length, which segments were cloned into the Promega vector pGL2 5' in front of the luciferase reporter gene.

5 The 8.5 kb SacI fragment which was subcloned from phage clone P12 was selected as the DNA source for the PCR amplification. In a final volume of 50 µl, 10 pmol of dNTP mix were added to 35 ng of this DNA, and a PCR reaction was carried out in 1xPCR reaction buffer (PCR-Optimizer kit from InVitrogen) and using one unit of

10 platinum Taq DNA polymerase (from Gibco/BRL). In each case 20 pmol of the 5' and 3' primers which are defined below were added as primers. The PCR was carried out in three steps. A two-minute denaturation at 94°C was followed by 30 PCR cycles in which the DNA was first of all denaturated at 94°C for 45 sec, after which the primers were annealed, and the DNA chain was extended, at 68°C for 5 min. The

15 cycles were concluded by a chain extension at 68°C for 10 min. The selected 3' PCR primer was in each case the primer PK-3A (5'-GCAAGCTTGACGCGCGCTGCCTGAAACTCG-3', position -43 to -65), which primer recognizes a sequence region 42 bp upstream of the ATG START codon. A promoter fragment of 4051 bp in size (NPK8) was amplified by combining

20 the PK-3A primers with the 5' PCR primer PK-5B (5'-CCAGATCTCTGGAACACAGAGTGGCAGTTTCC-3', position -4093 to -4070). Combining the pair of primers PK-3A and PK-5C (5'-CCAGATCTGCATGAAGTGTGTGGGGATTTGACAG-3', position -3120 to -3096) led to the amplification of a promoter fragment of 3078 bp in size (NPK15).

25 Use of the primer combination PK-3A and PK-5D (5'-GGAGATCTGATCTTGGCTTACTGCAGCCTCTG-3', position -2110 to -2087) amplified a promoter fragment of 2068 bp in size (NPK22). Finally, using the primer combination PK-3A and PK-5E (5'-GGAGATCTGTCTGGATTCTGGGAAGTCCTCA-3', position -1125 to

30 -1102) led to the amplification of a promoter fragment of 1083 bp in size (NPK27).

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The PK-3A primer contains a HindIII recognition sequence. The different 5' primers contain a BglII recognition sequence.

5 The resulting PCR products were purified using the Qiagen QIA quick spin PCR purification kit, in accordance with the manufacturer's instructions, and then digested with the restriction enzymes BglII and HindIII. The pGL2 promoter vector was digested with the same restriction enzymes, and the SV40 promoter contained in this vector was released and removed. The PCR promoter fragments ligated into the vector, which was then transformed into competent DH5 α bacteria (from
10 Gibco/BRL). DNA for the promoter activity analyses, which are described below, was isolated from transformed bacterial clones using the Qiagen plasmid kit.

Example 10

15 The activity of the hTC promoter was analysed in transient transfections in eukaryotic cells.

All the work with eukaryotic cells was carried out at a sterile workstation. CHO-K1 and HEK 293 cells were obtained from the American Type Culture collection.

20 CHO-K1 cells were kept in DMEM Nut Mix F-12 cell culture medium (from Gibco-BRL, order number: 21331-020) containing 0.15% streptomycin/penicillin, 2 mM glutamine and 10% FCS (from Gibco-BRL).

25 HEK 293 cells were cultured in DMOD cell culture medium (from Gibco-BRL, order number: 41965-039) containing 0.15% streptomycin/penicillin, 2 mM glutamine and 10% FCS (from Gibco-BRL).

30 CHO-K1 and HEK 293 cells were cultured at 37°C in a water-saturated atmosphere while being gassed with 5% CO₂. When the cell lawn was confluent, the medium was sucked off, after which the cells were washed with PBS (100 mM KH₂PO₄ pH

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7.2; 150 mM NaCl) and released by adding a trypsin-EDTA solution (from Gibco-BRL). The trypsin was inactivated by adding medium and the cell count was determined using a Neubauer counting chamber in order to plate out the cells at the desired density.

5

For the transfection, in each case 2×10^5 HEK 293 cells were plated out, per well, in a 24-well cell culture plate. The HEK 293 medium was removed after 3 hours. For the transfection, up to 2.5 μ g of plasmid DNA, 1 μ g of a CMV β -Gal plasmid construct (from Stratagene, order number: 200388), 200 μ l of serum-free medium and 10 μ l of transfection reagent (DOTAP from Boehringer Mannheim) were incubated at room temperature for 15 minutes and then dropped uniformly onto the HEK 293 cells. 1.5 ml of medium were added after 3 hours. The medium was changed after 20 hours. After a further 24 hours, the cells were harvested for determining the luciferase activity and the β -Gal activity. For this, the cells were lysed, at room temperature for 15 minutes, in the cell culture lysis reagent (25 mM Tris [pH 7.8] containing H_2PO_4 ; 2 mM CDTA; 2 mM DTT; 10% glycerol; 1% Triton X-100). Twenty μ l of this cell lysate were mixed with 100 μ l of luciferase assay buffer (20 mM Tricin; 1.07 mM $(MgCO_3)_4$; $Mg(OH)_2 \cdot 5H_2O$; 2.67 mM $MgSO_4$; 0.1 mM EDTA; 33.3 mM DTT; 270 μ M coenzyme A; 470 μ M luciferin, 530 μ M ATP), and the light generated by the luciferase was measured.

20

In order to measure the β -galactosidase activity, equal quantities of cell lysate and β -galactosidase assay buffer (100 mM sodium phosphate buffer, pH 7.3; 1 mM $MgCl_2$; 50 mM β -mercaptoethanol; 0.665 mg of ONPG/ml) were incubated at 37°C for at least 30 minutes or until a slight yellow coloration appeared. The reaction was stopped by adding 100 μ l of 1 M Na_2CO_3 , and the absorption was determined at 420 nm.

25

In order to analyse the hTC promoter, four hTC promoter sequence segments of differing length were cloned 5' in front of the luciferase reporter gene (cf. Example 9).

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The relative luciferase activities of two independent transfections in HEK 293 cells, using the constructs NPK8, NPK15, NPK22 and NPK27, are plotted in Fig. 11. Each experiment was carried out in duplicate. The standard deviation has also been given.

- 5 The construct NPK 27 exhibits a luciferase activity which is 40 times higher than the basal activity of the promoterless luciferase control construct (pGL2-basic) and from 2 to 3 times higher than that of the SV40 promoter control construct (pGL2PRO). Interestingly, a luciferase activity which was from 2 to 3 times lower than that obtained with the NPK 27 construct was observed in cells which were transfected
- 10 with longer hTC promoter constructs (NPK8, NPK15, NPK22). Similar results were also observed in CHO cells (data not shown).
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Patent Claims

1. Regulatory DNA sequences for the gene for the human catalytic telomerase subunit.
5
2. DNA sequences according to Claim 1, characterized in that the sequences are intron sequences in accordance with SEQ ID NO 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and/or 20 or fragments of these sequences which have a regulatory effect.
10
3. DNA sequences according to Claim 1, characterized in that the sequences are the 5'-flanking regulatory DNA sequence for the gene for the human catalytic telomerase subunit as depicted in Fig. 10 (SEQ ID NO 3), or fragments of this DNA sequence which have a regulatory effect.
15
4. Recombinant construct which contains a DNA sequence according to one of Claims 1 to 3.
5. Recombinant construct according to Claim 4, characterized in that it additionally contains one or more DNA sequences which encode polypeptides or proteins.
20
6. Vector which contains a recombinant construct according to Claim 4 or 5.
7. Use of recombinant constructs or vectors according to one of Claims 4 to 6 for preparing medicaments.
25
8. Recombinant host cells which harbour recombinant constructs or vectors according to one of Claims 4 to 6.
30

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9. Process for identifying substances which affect the promoter activity, silencer activity or enhancer activity of the human catalytic telomerase subunit, comprising the following steps:
- 5 A. adding a candidate substance to a host cell which harbours DNA sequences according to one of Claims 1 to 3, which sequences are functionally linked to a reporter gene, and
- B. measuring the effect of the substance on expression of the reporter gene.
- 10
10. Process for identifying factors which bind specifically to the DNA according to one of Claims 1 to 3, or to fragments thereof, characterized in that an expression cDNA library is screened using a DNA sequence according to one
- 15 of Claims 1 to 3, or subfragments of widely differing length, as the probe.
11. Transgenic animals which harbour recombinant constructs or vectors according to Claims 4 to 6.
- 20 12. Process for detecting telomerase-associated conditions in a patient, comprising the following steps:
- A. incubating a recombinant construct or vector according to Claims 4 to 6, which additionally contains a reporter gene, with body fluids or cell
- 25 samples,
- B. detecting the activity of the reporter gene in order to obtain a diagnostic value, and

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- C. comparing the diagnostic value with standard values for the reporter gene construct in standardized normal cells or body fluids of the same type as the test sample.

WO 99/33998

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Fig. 1

A

1 2 3 4 5 6 7 8 9 10



B

1 2 3 4 5 6 7 8 9 10



Fig. 2



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Fig. 3

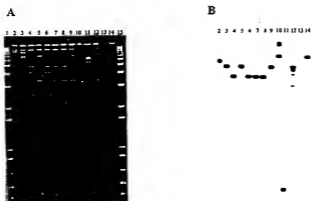


Fig. 4

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TCTCAAAAT	GTACCTTGAG	GTGATCGGCC	CACTGAGGCT	TCGCAAGATG	CTGGGATTAC	AGGCAATGAG	2450
CAGTCTGCTT	GGGCTATTGA	ACCAATTTAA	AACTTCCGCT	GGCTCAAGCT	ACACCGATCT	GTAAAGGATTT	2520
CAATGAGTTC	AAATTCGCTT	TTACTCAGGA	GTGACGCTCT	TTGTGATATT	TCTGTAAATG	CTTGAATGAT	2590
GGGATAGAGC	GCTCTCTGCA	CATATTCACA	GTCTCTGTGA	CCACTGTGTA	TGCCATAGGA	CGCATGTCAG	2660
GGCCAGCTGG	GAGGCTGCGAG	GCTTCAAGTC	CGAGTGGGCT	TGCCATGCTG	CAGTAAAGAC	GTGATGTAGA	2730
ATCGAGGCTC	AAATGTGAGC	ACTGTCTGTA	ATGTCATGAT	CTCAGTGTGT	SGTGAAGATAT	GTGAAGATTA	2800
AAGTCTCAGC	CTCTACTGCT	ACTGGGATTC	AGCGGCTTCT	CTATCGGCTC	CGAGGGGAGC	AGGATGCTCT	2870
CTCAGCTGTC	TGGAGGGAAG	AATGATACTT	TGTTATTTT	CAGTGTCTGT	ACTGAATGCA	CTGTTTCAAT	2940
TGTTGTGCTT	TGTTTGTGTT	CTGAGAGGCT	CTGCTACTCT	TGTTGGAGCT	CTGGAGGGGG	AAGTGTGCT	3010
CTGCGATCTG	CGCTACTCTG	CGCTGCTGCT	CGAGTCTTCA	GGTGAATCTG	CGTCTGCTCT	GGTGTGCTCT	3080
CGGCTTCAAC	ATGTTGTGAG	GGCTGTGCTG	GAGCTTGCTA	CTGACATGTA	TGCAGCTGCT	TGCTGCTGCT	3150
AAATGCTGTC	GATGATGAGT	GTGAGGCACT	ATGCGGAGCT	CAGAAATTAAC	TCTGTTTAGA	AACTATCTGG	3220
TGCTGAGTGC	GAGGCTGACC	CGACTCAAGT	GTGTTGGTGT	TTTAAAGCCA	TGATAGATCT	TTTTTATGTT	3290
TGTATAGACA	CTGTATAGTT	TTTACAGTCT	GATGATTAAG	ACATCAACAG	CTTTTCAAAG	ACAGATCTAC	3360
TGACCCGATA	ATATCTGGGT	GTCTTCTGGG	TATCAGCAAT	CTTATCTGAA	TGCGGGGAGG	CGTTCTCTCT	3430
CGATGCAAT	GGTGTGAATT	AGTCGAGCAT	AACTGTCGCT	TTCGATTTCT	TCTCTTCGCT	CTTTTAAATTT	3500
TGTTGTTGCT	AGTGTAGGCT	CTCTGCAGAG	AAACGATGTA	GTACTGTTCT	GTGAAATGAT	GGGATGATTT	3570
TTTCCAAAC	CGGCTCTTAC	CTGATGSCA	GAGACAACTA	ACAAAGACAG	CGCTTTAAAA	AGGCTTAGGG	3640
ATCATGATGG	GGATTCTTCA	AAGAGCGACC	TGTAAATCTA	ATGATTTACA	AGAGGAGGCT	ACCTCTCGAG	3710
GAGGCTGACA	CGCCAGGGAG	GCTGCGAGGC	CTGTTCAAAT	GTAGTCTGCA	TAAATAGAGG	AAATTCGCTG	3780
GGGAGTTTCT	GAAGATAGGA	AGGTGTGAGT	TTAAAGTTGC	GTGTTGTAGC	ATTCAGATGT	TTTTCAGGCT	3850
CAGTCTAGC	ATGCGGCAA	GCTCGGAGG	GAGCAGAG	CTTCTGCTCT	CTTCTGCTCT	AAATCTGAGC	3920
AACCTGAGAT	CTGGAATCTCT	GGGAAATGCT	CAGTGTCTCT	CGGTTGTGCT	CGGGGCTGCT	GCTGTGAGG	4000
GGACGATGG	CGGTGTGCTCT	TCTACTGCTG	GGCTGGAAT	CGGCTCTGCT	AGCTGTCTGAG	TGCGAGGCTT	4130
GGACCAAGGT	CGCTGGACCT	CGAGGCTGCT	CTGCAACCTG	TGCGGGCGGG	ATGTGACGAC	ATGTGGGCTCT	4200
CATCTGTGCG	ACAGATGTGC	GGGGCGGAG	GTCAAGGCTG	TGTTGGCTGG	TGTGAGGCTG	CGGGTGGGCT	4270
CGCCACAGGA	CGGCTTGGCT	CGATTTCCCA	CGCTTCTGCG	ACGGGACCTG	CGCGGTGGGT	GATTAACAGA	4340
TTTGGGGGTG	TTTGTGATG	GTGGGGAGCC	CTGCGGCTCT	GAGAGAGGCT	AAAGAGAAAT	GAGGGGCTCT	4410
TGTCAAGGAG	CGCAAGTGGG	GGGGAATGTC	TGCGAGGAGG	CAGTCTCGGA	GGTCCGCGCT	CGGCTGCTGAG	4480
GGGCAATGTC	GCTCTGCGCT	TGCTGCTGAG	CGGCTGTAC	GCTGCGCTCT	CGCTGCTGCT	ACGCTCGGCA	4550
TGTGTGCTG	CGGAGGCTCT	AGGCGCGGCT	TGCGAGGCTG	GAGGAGCGCT	TGGGTTGCTG	CATGAGGCTA	4620
CGGCTCAAG	GGTGGCGGCA	CGGACTGTTT	CGGAGGCTCT	CGGCTCTGCT	CGGCTCTGCT	CGGCTTACCT	4690

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Fig. 4 (Fortsetzung)

CAGAGCTAG	GCGGATGGA	CCTCTCTCG	CTGGGGCCCT	CGCTGGGCTC	CCTGCACCTT	GGGAGCGCGA	4760
CGGGCGCGCG	GGCGGGGAAG	CGCGGGCCAG	ACCGCCCGGT	CGGCGCGGAG	CAGCTGCGCT	GTGGGGGCGA	4830
GGCGGGGCTC	CCAGTGGATT	CGCGGGGACA	GACGGCCAGG	ACCGCGCTCC	CGAGCTGGCG	GAGGGACTGG	4900
GGACCGGGGC	ACCGTTCCTG	CGCCTTCACC	TTCAGACTCC	GGCTCTCTCG	CGCGGACCTC	GCGCGTCCCG	4970
GACCTCTGCC	GGGTCCCGGG	CGCAGCGCCC	TCCGGGCGCT	CGCAGGCGCT	GGCTTTGCTT	TCCCGGCGCC	5040
CGCTCTCTCC	TGCGGGGCGG	AGTTTCAGGC	AGCGCTGCGT	CCTGCTGCGC	AGGTGGGAAG	CCCTGGCGCC	5110
GGCGACCCCG	<u>GGGAGT</u>						5126

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Fig. 5

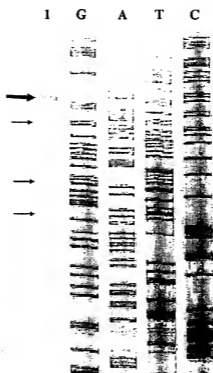


Fig. 6

GTTCACGGA	GGCTGGGTC	CTGCTGGCA	CGTGGGAAGC	CTGGGCCCCG	GGCACCCCCG	GGATGGCCGG	70
CGCTCCGCG	TGGCGAGCGG	TGGCGTCCCT	CTGGCGGAGC	CAGTACGGCG	AGGTGGTGGC	CGTGGCGAGC	140
TCTTGGGCG	CGTGGGCGCG	CGAGGGCTGG	CGGCTGGTGG	AGCGGGGGGA	CGCGGGGGCG	TTCGGGGCGC	210
TGGTGGCGA	GTGGCTGTGG	TGCTTGGCTT	GGAGCGAGCG	GGCGGGGGCG	GGCGGGCTCT	GTATGGGGCA	280
GGTGTGGCG	CTGAAGGAGG	TGTTGGGCGG	AGTGGTCCAG	AGTGGGGGCG	AGCGGGGGCG	GGATGGGGCG	350
CTGGGCTTGG	CTTGGGCTCT	CTTGGAGGGG	GGCGGGGGGG	GGCGGGGGCG	GGGTTTCAAG	AGCAAGCTGG	420
CGAGCTAGCT	GGCGAAGAGG	GTGACGGAGG	CAGCTGGGGG	GAGCGGGGGC	TGGGGGGTGG	TGCTTGGGCG	490
CGTGGGCGAG	GAGCTGTGGG	TTGACCTGGT	GGGAGCGTGG	GGGCTGTGGG	TGGTGGTGGG	TGGCGGGTGG	560
CGCTACGAGG	TGTGGGGGCG	GGCGCTGTAC	CAGCTGGGGG	CTGGCACTCA	GGCGGGGGCG	CGCGGCACAG	630
CTAGTGGAGC	CGGAAGGGCT	CTGGGATGGG	AAGGGGGCTG	GAACTACAGC	GTGAGGGAGG	CGTGGGGTGG	700
CTTGGGCTGG	CGAGGGGGCG	GTGGGAGGAG	GGCGGGGGGG	AGTGGCGAGC	GAACTGTGGC	GTTCGGGAGG	770
AGGCGGAGCG	TGGGGCTGGG	CGTTGGGCGG	GAGCGGAGCG	CGTTGGGCGA	GGGGTCTGGG	GGCGGCGGGC	840
CGAGGAGCGG	TGGAGCGGCT	GACCGTGGTT	TCTGTGGTGT	GTACCTGGCG	AGACCGGGCG	AAGAAGCGAC	910
CGCTTTGGAG	GGTGGCTGGG	CTGGGACGGG	CGACTGGCGC	CGATCGTGGG	GGCGGGGAGC	CGAGCGGGGG	980
CGCGACGCGA	CATGGGGGCG	AGGACGTGGC	TGGGAGACCG	CTTGTGGCGC	GGTGTAGGGC	GGAGGAGAGG	1050
AGTGTCTCTA	CGCTCGAGCG	GACAGGAGAG	AGCTGGGGCG	GTCTTGTCTA	CTGAGCTCTG	TGAGGGGGCG	1120
CTGTACTGGC	CGCTCGAGCG	TGCTGGAGAG	CAGCTTCTGG	GGTTCGAGCG	CGTGTAGTGG	AGGGATCTCG	1190
CGCAGCTTGG	CGCGGCTGGG	CGAGCGCTAC	TGGGAAGTGG	GGCGGCTCTG	TCTTGGAGCT	CTTGGAGAGC	1260
AGCGGCAAGT	CGCGTCTGGG	GTGCTGTCTA	AGACGCACTG	GGTGGCTGGA	GGTGGGCTCA	CGCGGAGGCG	1330
CGTGTCTTGT	CGCGGGGAGG	AGCGCGGAGG	CTCTGTGGCG	GGCGCGGAGG	AGGAGGAGAG	AGACCGGGCG	1400
CGCTGTGGTG	GAGCTGTGGG	CGAGCAGAGC	AGCGCGGGCG	AGGCTGGCGG	GGTGGTGGCG	GGCTGTGGTG	1470
CGCGGCTTGG	CGCGGGGAGG	CTCTGGGGCT	CGAGGACAGC	CGAGCGGGCG	TGCTGTGAGG	ACAGGAGAGG	1540
CTGTATCTTC	CTTGGGAGAGC	ATGGCGAAGT	CTCTCTGAGC	GAGCTGAGCT	GGAGAGTAGG	CGTGGAGGAG	1610
TGCGCTTGGC	TGGGCGAGAG	CGGAGGGGTT	GGCTGTGGTC	GGCGCGGAGG	GGACCTGTGT	CGTGGAGGAG	1680
TGCTTGGCGA	GTCTCTGAGC	TGGCTGATGA	GTGTGTAGCT	CTCTGAGCTG	CTGAGGCTGT	TCTTGGAGGT	1750
CAGCGAGAGC	AGCTTTGCAA	AAGAAGAGCT	CTTTTCTTAC	CGGAAGAGTG	TCTGGAGGCA	GTTCGAAAGT	1820
ATTGGAACTA	GACAGCACTT	GAAAGAGGTT	CAGCTGTGGG	AGCTGTGGGA	AGCGAGAGTG	AGGCGAGCAT	1890
GGGAAGCGCA	GGCGCTGGTG	GTGAGCTGCA	GGCTGGGTTT	CATCGGAGAG	CGTGGAGGGG	GGGCGGGAGT	1960
TGTGAAGATG	GATGAGCTTG	TGGAGGCGAG	AGCTGTGGCG	AGGGAAGAGA	GGGCGGAGAG	TCTGAGCTGG	2030
AGGCTGAAGG	CAGTGTGAGC	CGTGTGAAAG	TAGAGAGGAG	GGCGGGGGCG	CGGCTCTGTG	GGGAGCTGTG	2100
TGCTGGGGCT	GGAGGATGTC	CAGAGGGGCT	GGCGCACTTT	CGCTGGCTGT	GTGGGGGGCG	AGGAGCGGGC	2170
GGCTGGAGTG	TAGTTTGTGA	AGGTGGATGT	GAGGAGGGCG	TAGAGAGGCA	TGGCGTGAGG	CAGGCTGAGG	2240
GAGGTGATCG	CGAGCATGAT	CAAAAGCGAG	AGAGCTGATC	GGCTGGCTGG	GTAAGGGGTT	GTGGCAGAGG	2310
CGCGGCTATG	GGCGGTGGCG	AAGGCGCTCA	AGAGCGAGCT	CTGTACCTTG	ACAGAGCTTG	AGCGGTAGAT	2380
CGGACATGTC	GTGGGTGAGC	TGGGAGGAGC	CAGCGGGGCT	AGGAGTGGCG	TGCTGATGGA	CGGAGAGCTC	2450
TGCTTGAATG	AGGCGAGAGG	TGGGCTGTTC	GAGTGTGGCG	TAGGCTGTAT	GTGGCAGGAG	GGGTTGGGAG	2520
TGAGGGGCAA	GTCTGAGTTC	CAGTGGGAGG	GGATGGCGCA	GGGCTGATCT	CTCTGAGGCG	TGCTGGAGAG	2590
CGTGTGCTAC	GGGACATGGG	AGAGCAAGCT	GTCTGGGGGG	ATTGGCGGGG	ACGGGCTGCT	CTTGGGTTGG	2660
GTGGAGATGT	TCTTGTGGTG	GAGCGCTGAC	CTGACCGGCG	CGAAAGAGCT	CGTCAGGAGC	CTGTGTGGAG	2730
GTGTGCTGGA	GTAGGGTGGG	GTGGTGAAGT	AGTGGTGGG	AGTGGTGGAG	GTGGGCTGAG	GAGAGAGGCG	2800
CTGGGTGGCG	CGGCTGTGTG	TGCGAGTGGG	GGGCGGAGCG	CGATCGGCTC	GTGGGAGCTG	AGTGGGCTG	2870
AGCGGAGGCG	TGGAGTGGCA	GAGCGAGTCA	TGCGAGTATG	CGGGAGCTCT	CATCGAGAGC	ATTGTGAGCT	2940
TGAGGCGGGG	CTTGAGGGGCT	GGGAGGAGCA	TGCTGGGACA	ACTCTTGGGG	GTCTTGGGCG	TGAATGTGCA	3010
CAGGCTTGTG	CTGATTTTGA	AGGTGAACAG	CGTTCAGAGC	GGTTCAGGCA	AGATGTGACA	GATGTGTGTC	3080
CTGAGGCGCT	ACAGGTTTTC	CGGATGTGGT	GTGGAGCTTC	CATTTTCACTA	CGAAGTTTGG	AAGAAGGCGA	3150
CATTTTCTCT	GGGCTGTGAT	TCTGACAGGG	CGTCTGTGTC	CTACTGATCT	CTGAAAGGCA	AGAGAGCGAG	3220
GATTTGCTGG	GGGCGGAGGG	GGCGCGGGGG	CGCTGTGGCG	TGGAGGGGCT	GTGGGAGGCT	GTGGGAGGAG	3290
CAGTTCTGTC	TGAAGGTGAG	TGGAGAGCGT	GTGACCTGAG	TGGAGCTGCT	GGGCTGATCT	AGGAGAGGCG	3360
AGAGCGGAGG	GATGTGGGAG	CTCGCGGGGA	CGAGCTGAGC	TGGGCTGGAG	GGCGGAGGAG	AGCGGAGGCT	3430
GGCTCTGAGC	TTCAGAGGCA	TGCTGGAGTG	ATGGCACTCC	GGCCACAGCG	AGGCGGAGAG	CAGAGAGGAG	3500
CAGGCTGTTC	CGAGGAGGCT	CTAGCTGGCA	GGGAGGGGAG	GGGCGGGGAG	AGCGGAGGCG	CAGAGGCTGG	3570
GATTTGAGGG	CTTATGTGAG	TGTTTGGGCG	AGGAGGCTGAT	GTTCGGGCTGA	AGGCTGAGGT	TGGGGTGGAG	3640
GGTTCAGGCA	GTCTCAGGCG	AAGGGGCTGAG	TGTCAGGAGC	AGCTGGGCTG	TTTACTTGGC	CAGAGGCTGG	3710
CGCTGGGCTC	CAGCGAGGCG	CGAGCTTCTC	CTGCGAGAGA	GGCGGGGCTC	GATCTGAGC	ATAGAGAGAG	3780
TGCAATCCCA	GATTTGGGCT	TGTTCAAGCG	TGCGGCTGGC	CGCTCTGGCG	TTTGGAGGCG	AGCTGAGGAG	3850
TGGAGAGCTG	GAGAGAGGAG	CTGGAGAGCT	TGGGAATTTG	GATGAGGCAA	AGGTTGGGCG	GTATAGAGAG	3920
CGGAGAGCTC	CGAGCTGGAT	GGGCGTGGCT	GTGGGTGCAA	TGGGGGGGAG	GGCTGTGGGG	AGTAAAGATC	3990
TGAATATATG	AGTTTCTGAG	TTTTGAAAAA	AAAAAAGAAA	AAAAAAGAAA	AA		4042

Fig. 7

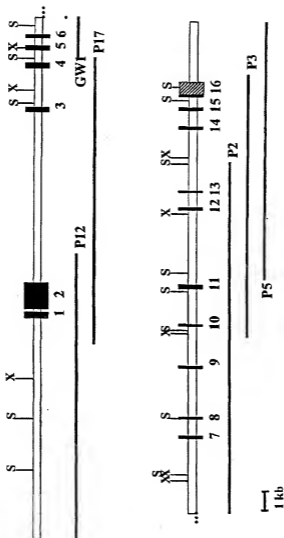
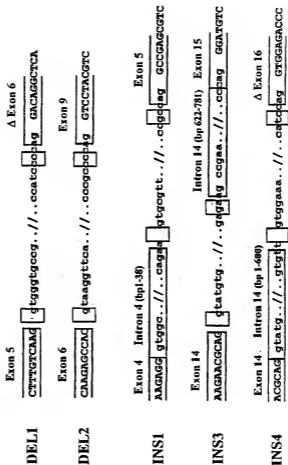


Fig. 8B



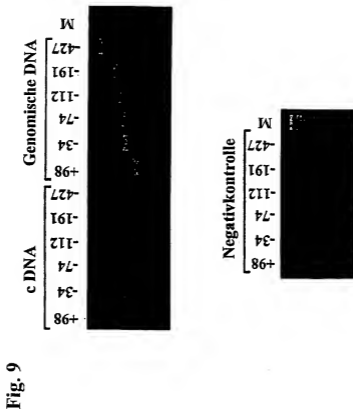


Fig. 10

ACTGAGCC	AAGAGTTC	GCTACGGT	AGCATGAT	GCACGAC	AGCCGAGCCT	TGGTACAGA	-11204
ATGAGCCGT	GTCCTAAJAA	AAJAAJAA	ATATATGGA	TCTTCTCGG	AGCTCTCTGA	AGCTCTCTGA	-11134
ACJAAACCG	AAATCAACGA	CAGAGGAA	TTTGAAATCT	ATACAAACAC	ATGAAATTA	ACATATATAC	-11064
TTCTGAATG	CCAGTGCTG	ATATGAGAA	TTAAJAAJGA	AATTAJAAJG	TTTATTTAG	CAATATATTA	-10994
CGGAAACATA	AGCTCTCAAA	ACCCAGGTA	TACAGCAAA	GCAGTGCTAA	GAAGGAATG	TATAGCTATA	-10924
AGCAGCTGA	CCAGAAJAA	AGAAJAGCCA	GGCCGCTGG	CTCATGCTGT	TAATCCGAG	ACCTTTGGAG	-10884
GGGAGGCGG	CGAGATGCG	TGAGTTCAG	AGTTCCAGAC	CAGCTGTACC	ACACAGAGGA	AACTTTGTCTG	-10784
CTACTAAJAA	TACAAJATTA	GCTGGGATG	GTGGCACTG	CCTGTATCTC	CAGCTACTGT	GGAGTCTGAT	-10714
CGAGGATAT	GCTGTGAAC	CAGGAGGTG	AGGTTGCGGT	GAAGCCGGAT	TGCGCCATTG	GACTCGAGC	-10644
TGGGTACAA	GAAGTAAC	CTGTCTCAG	AAAAAJAA	AGTGAJAA	ACTTAJAA	ACACCTAAT	-10574
GTGCGACTT	AAGTAAGT	AAJAGCAJGA	GCAACTTAA	CTAAATTTG	GTAAJAGAA	AGAAATTA	-10504
AGATTCAGAG	CAGAAJATTA	TGAATCTGA	AGATTAACAT	ACAAJAGTC	ACAAJATTA	AAAGTTGTT	-10434
TTTGAJAG	ATACCAJAA	TGACCAAC	TTTGCCAG	CATGAJAA	AGGAAGAG	ACCTAATTA	-10364
AAJATAGCT	AGATCAJAA	AGAGCAATTA	CACCTATATC	CACAAJAT	CAJAGATTA	CTAGAGCTTA	-10294
CTATGAGCA	CTGTACATA	ATAAJTTGA	AACTAGTA	AAATAGATA	AATTCCTGA	TGCATATAT	-10224
CTACCAJAG	TGAACATGA	AGAAJTCGA	AGCCCAJGA	GCACATAC	AATTAJTTGA	TAAAGCAT	-10154
AAJAAJAGT	CTCTAGCA	AGAGAGGCC	AGGCCCAAT	GGCTTCTG	CTGGATTTTA	CCATCATTT	-10084
AJAGAGAGT	GAATCTCAAT	CTACTCAAA	CTATTCTGA	AATAGAGGA	AGAAATCTT	CCAAATCAT	-10014
TTTACATGGC	CAGTATATC	CTGATCCAA	ACCCAGACA	AAJACATCA	AAJACAAJGA	AAJAAJAA	-9944
CAGAAJAGG	GAJATACGA	GGCAATATC	CCTGATGAT	ACTGATACA	AAATCTCTCA	CAJAAJCTA	-9874
GCJAAACCAA	TTACACACA	CCTCGAAG	ATCATTCAT	GTGATCAAT	GGGATTTAT	CCAGGAGTG	-9804
AGAGATGCT	CAAGATATG	AAATCAATC	ATGTGATCA	TGCTCCAC	AAATAGAT	ACAAJAACT	-9734
TATGATATT	TCATTTATG	CAGAAJAGC	ATTTGATAA	ATTTGACAC	CTCATGATA	AAJAACTCTA	-9664
AAJAAACGAG	TATACAGAA	ACATACAGC	CAGGCAAGT	CTGATCCAG	GCACCTTGG	GCACCTTGG	-9594
AGGCAAGGT	GGATGCTTG	CTGGGCGG	GGAGTTGAG	ACTAGCTGTG	GCACCAJAT	GAATCTGAT	-9524
CTCAJAAJAA	CTTTTAAJAA	AAJATAGCA	GCATGATG	CTATGCTGT	TATTCGAGG	TAGTCTGGT	-9454
CTGAGGTGG	GAJATCACT	TAGGCTAGG	AGGTGGAGC	TGCTGAGC	CATGAACCT	TCACTGATC	-9384
CCAGCTGAG	CACAGACAA	AGACCCACT	GAJTAGAG	AJAGAGAGG	AGAAAGGGA	AGGAGAGAG	-9314
AAJAGGAGAG	GAGGAGAGG	AGAGGTGGA	GGAGAGTG	AGGGGAGG	GGAAAGGAA	GAJAGAGAG	-9244
AGJAAJCTA	TTTCAACATA	ATAJAGGCC	TATATGAG	ACCGAGTAG	TATTTATGGG	AAJAACTGAA	-9174
AGCTTTCTCT	CTAAJATCTG	GAJATGACA	AGGGCCACT	TTACCACTG	TGATTCACCA	TAGTACTGAA	-9104
AGCTCTAGG	AGGCAATCA	GATAGAGAA	AGJAAJAA	GGCATCCAA	CTGAAJAGA	AGAGTCTGAA	-9034
TATCTCTGT	TGCAATGAT	ATGATCTAT	ATCTGGAJAA	GAJTTAGAC	ACCACTAAJAA	ACTATATTA	-8964
GCTGAATTT	GGTACAGCAG	GCACAAJAT	CAATGTACAA	AAATCAGTAG	TATTTCTATA	TTCCACAGC	-8894
AAJCAATCTG	AAJAAJAGC	CAJAAJAGCA	GCACAAATA	AAATTAACA	GCTAGJAA	ACCAJAAJAA	-8824
GTGAAGGTC	TCTACATGA	AAJCTATAA	ATGTTGATA	AGJAAATGA	AGAGGCAJCA	AAJAAJAGAA	-8754
AGATATCTA	CTCTATAGA	TTGCTGCA	AAATGCTTA	TAJATGCTA	TACTATCCCA	AGCAATATC	-8684
AAATCTAGT	CAATCTGAT	TAAJATCTA	ATGACTTCT	TACAGAAJAT	AGAGAAJACA	ATTTAAGAT	-8614
TTTACAGAA	GCACAAJAG	CCAGATAG	CCAAJGCTAT	CTGACCAJAA	AGAGCAJAA	CTGGAGCAT	-8544
CACATTAAC	GACTCTCAAT	TATACTACA	AGCTATAGA	ACCCAACTA	ACTGCTATG	GCATAAJAA	-8474
AGATGAGACA	GGTCCGAGG	GAJACGATA	GAJATCTAG	AAJCAAACTC	ATGCTATCT	AGTGAJCTCA	-8404
TTTTTGACA	AGGTGCCAG	ACATATCTT	GGGAAJAGA	TATCTCTCT	ATAJAAATG	CTAGGAGGA	-8334
CTGGATATGC	ATATGCAJAA	TAAJATATCT	AGAACTCTGT	CTCTCAJAT	ATCAJAAJAG	AAJCTCAJAT	-8264
GGATGAGAG	CTAAJATCTA	AAJCTCAJAA	CTTTGCACT	ACTAAJAG	AAJACCCGAG	AAJCTCTCA	-8194
GGATATGGA	TGCGGCAAG	ACTCTTTGAG	TAATTCCTG	CAGGCAJAG	CAJCAJAAJAG	AAJAAJAGAG	-8124
AAJTTGGGAT	ATATCAAGT	AAJAAJGCT	TGCCCAJCA	AGJAAJCAAT	CAJCAJAGAG	AGAGCAJAC	-8054
CCJAGGAATG	GGGATATAA	TTTGCAJCT	ATTCATCTAA	CAJGGAATTA	ATAJCCAGTA	TATATAGGA	-7984
CTGCAJATTA	CTCTATAAG	AAJACCACTA	ATAAGCTTT	TTTCAJAA	AGCAJAAJAG	TGCTGGTGA	-7914
CATTTCTGA	ATAGATCTAT	ACJAAJGGA	ACAGGCACT	TGAJAAJGCT	CTGACAGCA	CTGACATCA	-7844
AGCAJATGCA	AAJCAJATCT	ACTATAGAG	ATGCTCTAA	ACTGCTTTAA	ATGCTTTTA	TTCCAAJAG	-7774
GAGCAATAC	AAJTGCAAT	GAJAGATGG	ATAJAAJGA	ACCTTGGAG	ACTTTGGTG	GAATGGAA	-7704
TTGCTACCA	TATGAGAG	AGTTTGAJAG	TTCTCTCAJAA	AAJCAJAAAT	AAJCTTACCA	TACAGATCT	-7634
CCATGCTGAT	GTATATATCT	CAJAAJAGG	ATTCAGTGA	CTCAJAGCT	ATCTCCACT	CAJATTTAC	-7564
TGCAJGACTG	TTATATGAG	CCAGGTTTG	GAJGCAJCT	CAGTTTCCAT	CAJCAJAGCA	ATGAAJAG	-7494
AAJATGTGG	GCACATACAT	AAJGGATAC	TACGCAJCA	GAJAAJAG	TGAGTCTGT	TCAGTTCA	-7424
CAGCATGGG	GGCATGCTG	AGTATGTTAA	TGAJAAJAG	CAJGCAJAG	AGAGCAJAA	TTTCTATG	-7354
CTCCTCTAT	TGTGGGACA	AAJATTAJAA	CAJTTGACAT	AGJAAJAG	GAJAGTTGT	TTCTAGAG	-7284
GGTGGGGAG	AGGTAJCTA	GAJCTCAJCA	TAATTTATG	TATGTTTAA	ATAJCAJAA	AGAGTATAT	-7214
TGGGTTGTT	GTACACAJAA	GAJAGGATA	ATGCTTGAG	GTGATGATA	CCCATCTTA	CCGATATGA	-7144
TTTATAGCA	TGATATGCT	CTCATAAAT	ATCTCATGTA	TGCTATAGAT	ATAJCCCTTA	CTATATTA	-7074
AAJTAJAT	TTAATGGCA	GGCAGGTTG	CTCATCTG	TAACTCCAG	ACTTGGAG	CTGAGGCTG	-7004
GGATCTCAG	TGGGTGAGC	AGTTTGAJAG	CAGTCTGGC	ACCATGAG	AAJCCCTGCT	CTAAJAAJAG	-6934
TACAAJAT	AGCCAGGCT	GTGGCACT	ACCTGTAGT	CCATCTACT	AGGAGGCTGA	GACAGAGCA	-6864
TTGCTTGA	CTGGAGAGG	GAGGTTGAG	TGAGCCGAG	CTCATCTG	GCCTGAGC	TGCGGTGACA	-6794
GAGCAAGCT	CCATCTCAJAA	CAJAAJAGCA	AAJAAJAGAG	ATAJAAJATG	TAAJTTTAT	GTACCGTATA	-6724
CTATATATCT	CTCATATAT	AGAGTTTAA	AAJTAJAAJCA	ATTATAJAG	GTAAJTAAC	ACTTAATCTA	-6654
AAJTAJAGAC	ATGATATG	GGTTTCTAG	CTTCTGAG	AGTAJAAJAT	ATGGCCAG	TGCGCAJAT	-6584

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Fig. 10

GTGAGGAGCG	AACRGTGGA	GTACTGTTG	TTAGAGCCTC	ATACTCTCTG	TAAAGTCACT	AATTTTAACC	-6514
AAGACGAGCG	TGGGAGAGGT	TAAAGAGGCA	TCTATATAGC	CCTAAACAC	CTGCTAATAA	TGGTGAAGAG	-6444
TAATCTCTAT	TAATATACAA	TAATATACAG	TATCTCTAAA	ATCGAGCTCG	AGATTTGACA	CGTCTGATCA	-6374
GACGCTCTCT	TGATTCAGGG	TGCTTTTTTT	CTTGCTGTCT	TGAGAGATTT	CGATTTGTGT	TTCTGTGTTG	-6304
GTAAACCTTA	ATCTGTAAAC	ATCTGTAAAC	GAAJAAATGT	GTGATTTCTC	TCCAGAGAGA	TTAGAGTACG	-6234
TGGCAGGAG	CAGGCTGCTC	TGTGACCTG	AGCAGCTTCA	ATCTCTCAAG	GTCTCTGCTC	AGAGCCGAGC	-6164
TGCCAAGGAG	AGGCTGTGAT	ACCCAGGAGC	AGGAGAGCTC	GGATGGGAG	GGGCGATGAG	AGGCTGTGCT	-6094
CTCTGGTGAG	CGGCGCATGA	AGTGGCCCTTA	TTTACGCTTT	GCAAGATTTG	CTCTGGATAC	CATCTGGAAA	-6024
AGGCGGCCAG	CGGGAATGCA	AGGATCTAGA	AGGCTCTGCG	TCAAACCCAG	GCCAGCAGCT	ATGGGCGCCA	-5954
CCCGGGCGTG	TGCCAGAGGG	AGAGGAGTCA	AGGCGAGCTG	AGATATGGCT	TAAATCTTTT	TTTCACTCTGA	-5884
AGCAATGATC	AGGCTGTATT	CTGAGGGGAG	CTTGAGTTAG	GTGCTCTCTT	TAAACAGAGA	AGTCATGTAA	-5814
GACACCTCTG	CAGGAGGAAA	CCAGACGCCG	GGCTCTGGGT	CATTTTACTT	TTTCTCTCTT	CCCTCTCTTG	-5744
CCCTCTCGGT	TTCTGATCGG	GACAGAGTGA	CCGCGGTGGA	GGCTCTCGGA	CGGCTGTGAG	AGGACCTCTG	-5674
TGCCAAGGCG	TGCCAGACCC	CCGCGCTGAG	AGAGAGGGGT	CTGAGCTGTG	CTTAATATCA	AGCTGGGGTG	-5604
TGGCTGGGGG	CGGACAGGCA	CGGCGGGATT	CAAGACCTTA	ATTGATGAGG	TAATATGACG	CTTTCACAT	-5534
CCAAATGGGT	AAGACAGGAA	CTGAGCTATG	TTCTTAATTT	TCTCAATAAT	ACATTCAGGA	CTGCGAAT	-5464
ATTTTTCGCG	CTAAGTACTT	TTTATGGTT	TTCTAATGCT	GGCTTAGGGT	CGAGGGGAAA	GTACACGGGG	-5394
AGAGGGCTGG	CGGCGAGGGC	TATGAGCACG	CGAGGGCCAC	GGGGGAGAGA	GTCCCGCGGG	TGGAGGGCTG	-5324
ACAGCAGGAG	CAGTGAATGCT	CCTCGCTGGG	AGCTGCCACA	TGTGGGCAAG	CGAAGGCGGG	CGAGCTGGGT	-5254
TGATCTCAGG	ACCCATCATCC	GGCTCTCTGG	GGCCACCCAC	ACTAACCCAG	GAGATCAGGG	AGCTCTGAAC	-5184
CCGTGGGAAG	GAACATGACC	CTTGGCTGCG	TGCTTGGCTG	GGTGGGTCGA	GGGTATGAAA	GTGGGTGGCA	-5114
GGAAATGGCG	GTATAAATTA	CAGGACTCTG	CTGATGGGGA	CCGTTCTCTG	CATCATTTAT	CATCTCTCAC	-4974
CCCAAGAGCT	GAATGATTCC	AGCAACTCTT	TGGGTGTGGA	CAAGCCATGA	CAAACTCTAG	TACAAACAGC	-4904
AGCTCTTTAC	TAGGCCACCA	GAGCACGGGC	CACACCCCTG	ATATATTAGA	AGTCCAGGAG	AGATGAGGCT	-4834
CGTTTCAAGC	ACAGGCGCTG	GGTGACAA	CGGGCTGAAC	AGCTCTTTTC	TGTAGACTAG	TAGACCTCTG	-4764
CAGGCACTCT	ACCAAGATTCT	AGGCGCTGGT	TGCTGTCTTC	CAGGGGGGCG	ATCTGCGCTG	AGAGCTCTGG	-4694
CTGGGCTTCC	ACCATGGAGG	CAAGCTGTG	TCCAGACCTT	CGGGGCTGAG	CGCTGAGCTT	CTTCAACAGC	-4624
TTCTTAAGC	CGGCTGGGCG	CGGTTTCCAG	CGCTACTGTT	TCACCTCTCT	CAGCTGTCTT	TGCTTCAGCG	-4554
AGGTAGCTCG	CAGGGCTGCT	CTTCACATGG	GGGTGTCTG	TCCTTCCCCA	AGCATCATAT	CGGTGGAAG	-4484
GAGGAGATTT	TGGGCTCCG	AGACTGGCTC	CTTCCAGGCT	GAACCTGGCT	GGTGGGCCCG	AGTGGCAAGT	-4414
CTCTGGCTCG	GGCTGCAATG	TGAGCTCCAT	TTCCAGGCGC	TCCCGCTCTC	CTGTCACTTG	CCGGGGCTCT	-4344
CCGCTGTGTT	CTCTGTCTTC	TGTGCTCTT	TCCAGGTCCA	GGTGGGTGTT	TCTGTGCGCG	GTAGGGTCTC	-4274
GGGGTTTTTA	TAGGCTATGAG	ACGGGGGCGT	GGTGGGCCAG	GGCGCTCTTG	GGAAATGAAA	AGATTTGGGT	-4204
TGAAAGTAGG	AGGCGCTGTC	CTCACTTAGG	TCCAGGCGCG	CAGGCTCTGG	GATGGAGGCG	CCGCGAGGGA	-4134
CCGCGGCTCT	TCTGGGCCAGC	ACTTCTCTGC	CCGCTCTGCT	CTGGAGACCA	GATGGGACAT	TTCCACAGAC	-4064
ACTAAGCATC	CTTCTCCAAA	AAGACCCAGC	ATTGGACACC	CTGGACATT	GGCCACAGGC	CTGGGGAATT	-3994
AGCTG							
CAAGGAGGCT	CGGCACTCAT	GTACACATCT	CGGTGACAGA	CGGACCCCGG	CGTGTATTAT	TTAATAGCTA	-3924
CGAGGAGGCT	AAATCCCTGC	TAAATGTGCT	TTTAAACAA	TGGTAAACCA	AACGGGTGCA	CTCGACAGGT	-3854
GAGCTAAAGC	TCACAGTGAA	GAGGACATGT	CGGTTTATAA	CGCTCCAGGG	CATCTCAAGG	GAATTAAGCT	-3784
GAGTCTAAAG	TGCCAGCTCC	ATGGATACG	TACGCAACAT	AGCTCAAAAG	AAGAAATTTG	ACCCGAGGCT	-3714
AGGGGAGTGG	TAAAGGAGGT	TAAAGGAGGT	GGGGCGGCGA	CGTGGGGGCT	ACTCGACGCA	CTCTTTTACT	-3644
AAGCCAGTTT	ATGGTGTCTG	ATGGTATTGG	CTCAGTTATG	GGAGACTAAC	CATAGGGGAG	TGGGGATGGG	-3574
GAACCCCGGA	GGCTGTGGCA	TCCTTGGCAT	GGCGGAGTGT	CTGGGCGAGT	ATAATGCTCT	AGAGATGCCG	-3504
ACGTCTGTAT	TCCGCCAACCA	CTGTGGACAG	AAGCCCGCGG	GGCCGAGGCG	CTTTCAGGTT	GTATCTCTCG	-3434
TGGAGGCTCT	GAGGTGTGAT	ATCTTCCGG	ACTACTGTGA	GGCCCGGAAA	GTAATCCAGG	GGTCTTGGGA	-3364
AGAGGGCGGC	AGAGGGGTGA	GAGGGGGGCA	GCTCTCAGAC	GATGGAGGCA	CTCASTCTGA	GGTCTGAAGG	-3294
GGAGGGAGGG	CTTCCAGCCC	AGGCTGTGAA	GGCTCTCCAG	AGGCTGGAAA	AGCGGGGAGG	GGGACCTGCT	-3224
AGGAGGCTGT	CAGGAGGAG	GCAAGGCTGAG	CGCTTAGGCC	ACCGGGGCGC	ATGGTGGAGC	TGGGGCTCTC	-3154
GTGCGATAGG	AGGGCAGTGG	CGCTGGCTTT	CTAGCATGAA	GTGTTGGGGG	ATTCTCGAAA	CATGGGCTGA	-3084
ACCATGTCAG	TGTGATCTTA	GGGAGGAGCA	AGTGAATTTA	TTTATGACTT	TTATTTAGAT	TAAGGCTCTA	-3014
CGTCTCTGCG	GTATGCTCTT	TGTTGCCAG	CGTGGAGTGA	AGGGGCACTA	TCTTGGTCTA	CTGCAACTCT	-2944
CGTCTCTGGA	TTCTGAGCAA	TTCTGCTGCC	TCAGGCTCCG	AGTAGTGTGG	GATTTGAGCG	GTGGCAGCAG	-2874
AGACCCGGCT	AATTTTGGAT	TTTATGAGA	GATGGGCTTT	CACCATTTTG	GTCAAGGTGA	TCTCAAAATG	-2734
CTGACCTCAG	GTATCTGCCG	CACCTCAGCC	TCCCAAGGTG	TGGGGATGAC	AGGCAATGAG	CAGTGCAGCT	-2664
GGCTATTATTA	ACCATTTTAA	AACTTCCCTG	GGCTCAGTCT	AGACCCAGCT	GTAAGGAGTT	CATGGAGTCT	-2594
AATTTCCCTG	TTACTCAGGA	GTACCTCTCC	TTTGAATTT	TTCTGTAAT	TTGTAGAGT	GGGGATGACG	-2524
CGTCTCTGGA	CATATTCACA	GTCTTCTGTA	CGACTGTGTA	TCCCATGGGA	CCGACTGTGAG	GGGCGAGCTG	-2454
GAGGCTCTGAG	CGTTCAAGTCT	CCAGTGGGGT	TGCCATCTCG	CAGTAGAAC	CTGATGTGAG	CTAGGGGCGC	-2384
AGATGTGTGAG	ACTGCTGTGA	ATCTCAATGT	CTCAGTGTGT	GCTGAAGACT	TGAGAAATTA	AGTGTGATCT	-2314
CTCTAGTCTC	ACTGGGATTTG	AGGCGCTTCC	CTGATCCGCC	CAAGGGGCGG	AGAGATCTCT	CGCTCAGCTG	-2244
TGGGAGGAG	AATGATACTT	TGTTATTTCT	CAGTGTCTCT	ACTGAACTCA	CTGTGACTT	TGTTGGTGTG	-2174
TTTGTGTTCT	TGTTGAGGCG	GGTTTCACTT	TTGTGCTCA	CGTGGAGGAG	AGTGGCAATG	CGGATCTGTT	-2104
GCTTATGCTA	CGCTCTGCTC	CCGAGTTTCA	AGGATTTCTC	CTGCTCTGCG	GTCCCATTTG	CTGGGATTTA	-2034
CAGGCAACCG	CCACCATGCC	CAGCTAATTT	TTTGTATTTT	TAGTAGAGAC	GGGGGTGGGT	GGGTTCTACC	-1964

Fig. 10

ATGTTGGCCA GGCTGCTC GAACCTCTGA COTCAGATGA TCACCTGCC TCTGCCTCT AAAGTCTGG -1894
 GATTACAGGT GTGAGCCACG ATGCCGAGCT CAGAAATTAC TCTGTTTGA AACATCTGG TCTGAGTAG -1824
 GAAGCTCACC CCACCTCAAGT GTTGTGGTGT TTAACCCA ^{CAAT-Box} TATAGAAIT TTTTATITGT TGTTAGAACA -1754
 CTCTTGATGT TTTACACTGT GATGACTAAG ACATCATCAG CTITTCAAAG ACACACTAAC TGCACCCATA -1684
 ATACTGGGGT GTCTTCTGGG TATCAGCAAT CTTCATTGAA TGCGGGGAGG CGTTTCTCGT CCATGCCAAT -1614
 GGTGTTAATT ACTCCAGCAT AATCTTCTGC TTCCATTCTC TCTCTCCCT CTTTTAAAT TGTGTTTCT -1544
 ATGTTGGCTT CTCTGCAGAG AACCAGTGA AGCTAGAACT TAACCTTTGT TGGAACAAT TTTCCAAGC -1474
^{Sp1}
GGCGCTTTGC CCTAGTGCCA GAGACAATTC ACAACACAG CCGTTTAAAA AGGCTTAGGG ATCACTAAGG -1404
 GGATTTCTAG AAGAGGAGCC TGTAACTCTA AGTATTTACA AGAGAGGGCT AACCTCCAGC GAGCGTGACA -1334
 GCCCAGGGAG GGTGCGAGGC CTGTTCAAA GTTAGCTCCA TAAATAAAGC AATTTCTCCG GGCAGTTTCT -1284
 GAAAGTAGGA AAGGTTACAT TTAAGGTTGC GTTTGTTAGC ATTTCACTGT TTGCGACAGT GAGTACAGCG -1194
 ATCCTGCGAA GGCCTCGGGA GAGCCAGAAG TTTCTCGCC CCTTAGATCC AAACCTTAGC AACCCGAGGT -1124
 CTGGATTCTT GGGAACTCTT CAGCTGTCT GGGGTGTGCG CGGGGCCCCA GGTCTGAGAG GAGCCAGTGG -1054
 CGGTGTGCTT TCTACTGCTG GGCTGGAAGT CGGGCTCTCT AGCTCTGCAG TCCGAGGCTT GAGCCAGGT -984
 GCCTGGAACC CGAGGCTGCC CTCCACCCTG TCGCGGCGGG ATGTGACCAG ATGTTGGCTT CATCTGCCAG -914
 ACAGAGTGCC GGGGCCGAGG GTCAAGGCCG TTGTGGCTGG TGTGAGGCGC CGGATGCGCG GCGACAGAGA -844
 CGGCTGTGCT CCAATTCCCA ^{CCAC-Box} CCGTTTCTCG ACGGAGCG ^{Sp1} CCGGTGGGT GATTAAACAGA TTTGGGTTGG -774
 TTTGTCATG GTGGGGAACC CTGCGCGCTT GAGAACTGCG AAGAGAAAT GACGGGCTCT TGTCAAGAG -704
 CCCAAGTCCG GGGGAAGTGT TGCAGGGAGG CACTCCGGGA GGTCCCGGCT GCGCTCCAG GAGCAATGC -634
 GTCTCTGGGT TGTCCCCA ^{AP-2} CCGTCTAC GCGGCTCGGT CCGTCCCTTC AGCTCGGCA TTTGTTGTCG -564
 CGGAGCCCGC AGCGCCCGCG TCCGAGCTG GAGGCAGGCC TGAGTCTCGG GATCAGGCCA GCGGCCAAG -494
 GGTGCGCGCA GSCACTGTT CCGAGGGCT CCAATCATG GCGGCTCCCT CGGTTACCC CACAGCTAG -424
 CGGAAATGCA CTCTCTCGCG CTGGGGCCCT GCGTGCGCT CCGTCACTCT GGGAGCGGGA GCGGCGCG ^{Sp1} -354
GGCGGGGAAG CGGGGCCAG ACGCCCGGCT CGCGCGGGAG CAGCTGCGCT GTCGGGGCCA GCGCGGCTC -284
 CTAGTGGATT GCGGGCCACA GAGCCGAGG ACGCGGCTCC CGACGTGCG ^{c-Myc} GAGGAGCTGG GGACCGGGC -214
 ACGGCTCTCG CGCCTTCAGC TTGCACTGCG GCGTCTCGG CGGGAGCG ^{Sp1} GCGGCTGCG GAGCCCTCCC -144
 GGTGCCCGG CGCAGCCGCC TCGGGGCTCT CCGAGCCCT CGGCTTCTT ^{Sp1} TCGGGGCTCG CGGCTCTCC -74
TCCGCGCGCG ^{c-Myc} AGTTTCAGGC AGCGCTGCTT CTTGCTGCG ACGTGCGAG ^{c-Myc} CCGTGGCCCC GCGCAGCCCC -4
 GCGATG

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